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Transformation of nanoparticles into compacts: A study on PLGA and celecoxib nanoparticles

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ABSTRACT

Oral delivery of nanoparticles possesses many advantages for delivery of active pharmaceutical ingredients (APIs) to the gastrointestinal tract. However, the poor physical stability of nanoparticles in liquid state is often a challenge. Removing water from the nanosuspensions and transforming the nanoparticles into solid particulate matter in the form of, e.g., tablets could be a potential approach to increase the stability of nanoparticles. The aim of this study was to transform nanoparticles into compacts and to investigate the redispersion of nanoparticles from compacts as well as the dissolution behavior of these compacts. DL-lactide-co-glycolide copolymer (PLGA) nanoparticles and celecoxib (CLX) nanoparticles were used as two model nanoparticle systems and fabricated into nano-embedded microparticles (NEMs) and subsequently compressed into compacts. The compacts were evaluated with respect to the redispersibility of the nanoparticles, as well as the dissolution characteristics of CLX. The results showed that the NEMs could be readily compressed into compacts with sufficient mechanical strength. The size of the redispersed PLGA nanoparticles from the compacts using 2-hydroxypropyl-β-cyclodextrin (HPβCD) as stabilizer was comparable to the original nanoparticles. In contrast, the redispersibility of CLX nanoparticles from the compacts was not as effective as for the PLGA nanoparticles evidenced by a significant increase in the size and polydispersity index (PDI) of the redispersed nanoparticles. Nonetheless, an obvious enhancement in dissolution rate of CLX was observed from the compacts with CLX nanoparticles. It is concluded that transforming polymeric nanoparticles into compacts via NEMs provides stabilization and allows redispersing original nanoparticles. Despite the reduced redispersibility, compacts loaded with nanoparticles exhibited improved dissolution rate compared with the crystalline drug. Loading of nanoparticles into compacts is a promising approach to overcome the poor stability of nanoparticle within oral drug delivery of nanoparticles.

1. Introduction

Nanoparticles possess many advantages in pharmaceutical drug delivery such as protection of the encapsulated drug, sustained drug release, overcoming biological barriers and improving oral bioavailability of some hydrophobic drugs (Wilczewska et al., 2012). With these benefits, nanoparticles have been extensively studied for enhancing the treatment of many diseases such as cardiovascular diseases, respiratory diseases, cancer and diabetes (Godin et al., 2010; Pison et al., 2006; Shi et al., 2017; Veiseh et al., 2015). Despite the fact that most marketed nano-formulations are administered as injectable products, the transformation of the nano-formulations into oral products has many advantages. For example, the delivery of biologics through nanoparticles for the treatment of chronic diseases could improve efficacy and patient compliance (Pridgen et al., 2014). The release of nanoparticles in the gastrointestinal (GI) tract could benefit the treatment of local intestinal diseases with tunable release properties (Kotla et al., 2019). In addition, by formulating into nanoparticles, the dissolution of many hydrophobic drugs in the GI tract could be improved (Hu et al., 2004).

The currently used methods for preparation of nanoparticles such as nanoprecipitation, emulsification-solvent evaporation, nano-complexation as well as wet milling and high-pressure homogenization result in an aqueous suspension, which may have various critical issues related to physical and even chemical stability of the nanoformulations including sedimentation, agglomeration, crystal growth and hydrolysis of the loaded drugs (Wu et al., 2011). These instability issues have
limited the industrial and clinical applications of the aforementioned nanoformulations although with many advantages over conventional formulations. Removing water from the colloidal systems could improve the physical and chemical stability of the nanoformulations, and the resulting solid products could be further processed into oral drug products such as capsules and tablets. Spray drying is one of the most commonly used method to remove water from nanosuspensions to produce nano-embedded microparticles (NEMs). Stabilizers are often used in the spray drying process in order to preserve the advantages of the nanoparticles, and to avoid nanoparticle aggregation upon drying. Studies have shown that trehalose and mannitol were effective stabilizers for spray dried nanoparticles (Torge et al., 2017; Ruge et al., 2016), and the ratio between nanoparticles and excipients is very important.

The spray dried NEMs can be further processed into compacts that are composed of nanoparticles. The poor stability of nanoparticles in suspensions could be addressed by transformation into compacts. The stabilizers used in spray drying typically form bridges between nanoparticles, which can reduce the interaction between nanoparticles and facilitate the redispersion of nanoparticles from the compacts (Li et al., 2021). In addition, the high density of the compacts can be utilized for the improved delivery of nanoparticles at high doses, especially compared with liquid suspension but also free powders and powder-filled capsules. Additionally, it has been reported that the high density allows the compacts to sink to the bottom of the stomach or intestine, allowing a good contact of the compacts with the surrounding gastrointestinal tissue. This further increases the chance of getting biologics and other molecules across the tissue due to the high local drug concentration achieved to a liquid or granules (Tripathi et al., 2019).

In this study, dispersible compacts of nanoparticles intended for oral delivery of nanoparticles were prepared using two types of model nanoparticles, i.e. poly (lactide-co-glycolide) (PLGA) nanoparticles and celecoxib (CLX) nanoparticles. 2-hydroxypropyl-β-cyclodextrin (HPβCD) was used as a stabilizer and disintegrating agent to obtain PLGA NEMs or CLX NEMs by spray drying, followed by compaction into compacts (Fig. 1). The impact of stabilizers on the redispersion of PLGA nanoparticles or CLX nanoparticles from the NEMs and the compacts was studied using dynamic light scattering (DLS). Scanning electron microscope (SEM), X-ray powder diffraction (XRPD), Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and Raman spectroscopy were used for the investigation of the different physiochemical characteristics of the NEMs prepared from PLGA nanoparticles and CLX nanoparticles. The mechanical properties of the compacts made of polymeric nanoparticles and drug nanoparticles were compared. The redispersion of nanoparticles from the compacts and the dissolution profile of CLX from the compacts of nanoparticles were also investigated. The results indicated that nanoparticles could be transformed into compacts with good mechanical strength and redispersibility, and this will benefit the development of orally delivered nanoparticle products.

2. Materials and methods

2.1. Materials

DL-lactide-co-glycolide copolymer (PLGA, PURASORB® PDLG) was purchased from Corbion (Amsterdam, the Netherlands). Celecoxib (CLX) was acquired from Dr. Reddy’s Laboratories Ltd. (Hyderabad, India). 2-hydroxypropyl-β-cyclodextrin (HPβCD) were purchased from Sigma-Aldrich (Copenhagen, Denmark). Kollidone VA64 (PVPVA) was obtained from BASF (Ludwigshafen, Germany). Silicified microcrystalline cellulose (SMCC) and sodium starch glycollate (SSG) was purchased from JRS PHARMA (Rosenberg, Germany).

2.2. Methods

2.2.1. Preparation of nanoparticles

PLGA nanoparticles and CLX nanoparticles were prepared by microfluidic mixing in a 3D printed microfluidic chip with a channel diameter of 380 μm (Li et al., 2020). For the preparation of PLGA nanoparticles, 10 mg/ml PLGA was dissolved in acetonitrile and injected with a syringe pump (Harvard Apparatus 11 Elite) into the center inlet of the microfluidic chip at 1 ml/min, and water was injected from the two side inlets at a flow rate of 5 ml/min each. The PLGA concentration in the nanosuspension was 1 mg/ml. For the preparation of CLX nanoparticles, 25 mg/ml CLX was dissolved in ethanol and injected with a syringe pump into the center of the microfluidic chip at 0.2 ml/min. In addition, 0.2 mg/ml PVPVA solution was injected from the two side inlets at 3.5 ml/min each. The CLX concentration in the nanosuspension was 0.7 mg/ml.

2.2.2. Spray drying of NEMs with PLGA nanoparticles/CLX nanoparticles

HPβCD was dissolved in Milli-Q water and mixed with the PLGA nanosuspension or CLX nanoparticles and then spray dried using a Büchi mini spray dryer B-290 (Büchi Labortechnik AG, Postfach, Switzerland). The final concentration of PLGA was 33% (w/w) and the final concentration of CLX was 10% (w/w) in the spray dried NEMs, respectively. The following parameters were used for spray drying: inlet temperature 85 °C, outlet temperature around 38 °C, feed rate 4.5 ml/min, atomizing air flow rate 473 L/h, compressed nitrogen flow rate 35 m³/h. Spray dried NEMs were collected and stored in a desiccator under room temperature before characterization.

2.2.3. Scanning electron microscope (SEM)

The morphology of raw materials and spray dried NEMs were studied using Scanning Electron Microscope (SEM, Hitachi TM3030 Tablettop, Japan). Samples were mounted on double-sided adhesive carbon tape on aluminum stubs and then coated with gold layer under vacuum using an auto sputter coater (108 auto, Cressington) for 30 s. The morphology of spray dried NEMs was then visualized at an acceleration voltage of 15 kV under charge-up reduction mode.
2.2.4. X-ray powder diffraction (XRPD)

The solid state characteristics of spray dried NEMs was assessed with an X’Pert Pro MPD X-ray diffractometer (PANalytical, Almelo, The Netherlands) using CuKα radiation (45 kV, 40 mA, λ = 1.5418 Å). The samples were placed on a zero-background aluminum holder and scanned under reflection mode in a 20 range from 5 to 35° at a rate of 0.067° 2θ/s and a step size of 0.026° 2θ. Data was collected and analyzed using the X’Pert Data Collector software (PANalytical).

2.2.5. Differential scanning calorimetry (DSC)

Thermal analysis of the spray dried NEMs was performed with a Discovery DSC (TA Instruments, New Castle, USA) under modulated temperature mode. Approximately 2 to 6 mg samples were weighed in an aluminum Tzero pan and sealed with a lid before being heated from 35 °C to 60 °C at a heating rate of 2 °C/min with an amplitude of 0.2120 °C and a period of 40 s. Thermograms were analyzed with Trios software (version 3.3, TA-Instruments-waters LLC, New Castle, DE, USA), the glass transition temperature was determined as the midpoint of the onset and endset temperature. The melting point was determined using the X’Pert software (version 3.3, PANalytical, Almelo, The Netherlands).

2.2.6. Fourier-transform infrared (FTIR) spectroscopy

FTIR Spectrometer (Bomem, St-Laurent, Canada) was used to investigate the absorption peaks of the raw materials and NEMs. Spectra of the raw materials and spray dried NEMs with or without HPβCD as stabilizer was collected at wavelengths from 600 to 4000 cm⁻¹ with the GRAMS AI software (Thermo Scientific, Waltham, USA). The resolution was set as 2 cm⁻¹, scan number was set as 64.

2.2.7. Raman spectroscopy

The Raman reflection of the original materials, PLGA and CLX, the spray dried powders of the nanoparticles with or without HPβCD were collected with a Kaiser RXX1 Microprobe from Kaiser Optical Systems (Ann Arbor, MI, USA) equipped with a PhAT probe set up in a reflection Raman configuration. The exposure time was 5 s, and 5 accumulations were averaged for each spectrum.

2.2.8. Compacting and mechanical properties of the compacts

Spray dried CLX NEMs/PLGA NEMs were mixed with silicified microcrystalline cellulose (SMCC) or sodium starch glycolate (SSG) at a weight ratio of 1:1.50 mg of the mixed powders were compressed with a 6 mm punch using a single punch tablet press (Gamlen Tabletting Ltd., UK), fitted with a 500 kg load cell (CT6-500-022) at compression pressures of 35, 70, 105 and 140 MPa. The content of PLGA in a single compact was 8.25 mg, and the content of CLX in a single compact was 2.5 mg. The breaking force of a compact was measured with a tablet hardness tester (8 M, Dr Schleuniger, Switzerland). The tensile strength was calculated with Eq. (1).

\[
\text{Tensile strength} = \frac{2F}{\pi D T}
\]  

(1)

where \(F\) is the breaking force (N), \(D\) is diameter (mm) and \(T\) is the thickness (mm) of the compacts.

The true density of the compacts was measured with a helium pycnometer (AccuPyc II 1340, Micromeritics, US) using a 3.5 cm³ chamber insert. A pressure of 18 psig and 10 cycles were used for the determination. The density of the compacts was calculated with the weight and the volume of the compacts. Solid fraction was calculated with Eq. (2).

\[
\text{Solid Fraction} = \frac{\text{Tablet density}}{\text{True density}}
\]  

(2)

2.2.9. Redispersion of nanoparticles from NEMs and compacts

The compacts of nanoparticles were disintegrated in 10 ml Milli-Q water in 15 ml Eppendorf tubes and rotated with a rotator (Stuart rotator SB3, Staffordshire, UK) for 20 min to achieve fully disintegration. The suspension was left for 20 min and the supernatant was measured for particle size and PDI by DLS with a Zetasizer Nano ZS (Malvern Instruments, Worcestershire, UK) equipped with a 633 nm laser and 173° detection optics. 5 mg of spray dried NEMs containing either PLGA nanoparticles or CLX nanoparticles were resuspended while stirring in 5 ml Milli-Q water, the size and PDI were measured by DLS as well. All the redispersion studies were performed in triplicate.

2.2.10. Dissolution of CLX from compacts

The dissolution profile of the compacts of CLX nanoparticles compressed with SMCC or SSG were investigated in comparison with compacts compressed from spray dried NEMs without fillers. Compacts compressed from physical mixture of CLX raw material and SMCC or SSG were used as controls in the dissolution study. Dissolution test of the compacts was performed in 200 ml 0.05 M PBS (pH 6.8) at 37 °C using the paddle method with a rotation speed of 150 rpm. 3 ml samples were withdrawn and replaced with 3 ml PBS at predetermined time points (20, 30, 45, 60, 90, 120, 160, 220, 310, 400, 490 and 580 min). The concentration of CLX in the dissolution medium was measured with HPLC (LC 1260, Agilent Technologies, Santa Clara, CA, USA) on a C18 column (Phenomenex, 100 mm × 4.6 mm, 5 µm), the mobile phase used for the analyses was acetonitrile: water = 1:1, flow rate was 1 ml/min and a UV detection wavelength of 256 nm was used.

3. Results and discussion

3.1. Morphology and size of spray dried NEMs

The morphology of the raw materials i.e. PLGA and CLX and the spray dried nanoparticles with or without HPβCD is shown in Fig. 2. PLGA as a raw material had a chunky morphology before spray drying and the size of the original PLGA particles was larger than 100 µm. The PLGA nanoparticles spray dried without HPβCD showed a narrow size distribution, with size around 2 µm. The majority of the particles were agglomerates. When spray dried with HPβCD, the size distribution of the PLGA NEMs became broader compared with spray dried PLGA nanoparticles. Based on the SEM observation, some of the large microparticles were around 10 µm while most were around 2 µm. The surface of some microparticles appears collapsed, which was similar to the microparticles previously reported (Li et al., 2019). Other stabilizers such as trehalose, mannitol and polyvinylpyrrolidone (PVP) were also investigated in the spray drying process (Fig. S1). It could be observed that NEMs with PVP as stabilizer had a dimpled appearance on the surface similar to the NEMs with HPβCD. This can be explained by the high Peclet number of HPβCD and PVP in nanosuspensions, where the movement of solutes is slower relative to the receding surface of the droplets, resulting in a collapsed appearance (Ye et al., 2015; Vehring, 2008; Li et al., 2015). The size of NEMs with PVP was smaller and more homogenous compared with the NEMs with other stabilizers. However, PVP has a tendency to absorb a high amount of water compared to the other stabilizers investigated (Fig. S2). Therefore, it was not chosen as the stabilizer in the subsequent compacting process.

CLX raw materials had a plate-like morphology before spray drying, typical for the crystalline material. The size of spray dried CLX nanoparticles was around 10 µm with a spherical shape, and some needle-like particles could be observed. After spray drying with HPβCD, the size of the NEMs decreased to around 1 to 2 µm, presenting a more collapsed morphology. It was noted that the size of CLX nanoparticles without HPβCD was obviously larger than CLX-NEMs with HPβCD, while PLGA-NEMs have similar particle sizes regardless of addition of HPβCD or not. This is explained by the aggregation and growth of CLX nanoparticles in microparticles upon evaporation of the solvent (Paradkar et al., 2002). However, PLGA nanoparticles often possess high surface charge which helps prevent the aggregation of nanoparticles (Fonseca et al., 2002). Therefore, the size of spray dried PLGA nanoparticles was relatively small compared with spray dried CLX nanoparticles. With the
addition of HPβCD, the contact among CLX nanoparticles could be prevented and crystal growth slowed during the drying process. Hence, smaller microparticles were observed with HPβCD.

3.2. Solid state characteristics of spray dried NEMs

The solid state characteristics of PLGA raw material, CLX raw material, spray dried PLGA nanoparticles, and CLX nanoparticles as well as the NEMs are shown in Fig. 3. Spray dried PLGA nanoparticles were amorphous regardless of using HPβCD or not. CLX as a raw material was crystalline. After spray drying of the CLX nanoparticles (without HPβCD), there was still some residual crystallinity based on the analysis of the diffractogram. The main diffraction features of spray dried CLX nanoparticles were at 16.7, 22.4, 26.2° (2 theta), which were not identical with CLX raw material. This is an indication of the polymorphic change of CLX crystals from the stable polymorphic form III (Chawla et al., 2003). It has been reported previously that precipitation of CLX from a polysorbate 80 solution resulted in a polymorphic form IV (Lu et al., 2006), which has the same main diffraction characteristics as spray dried CLX nanoparticles. The thermal analysis results (Fig. 4) also indicated similar solid form changes of the PLGA and CLX after spray drying. All samples containing PLGA showed obvious glass transition on the thermograms, which indicated the amorphous state of PLGA-NEMs. The glass transition (T_g) of PLGA after spray drying (PLGANP) showed a slight increase from 44 to 47 °C compared with the PLGA raw material, the possible reason might be that PLGA was dissolved in a good solvent i.e. acetonitrile, and resulted in PLGA powder with high density after spray drying (O’Addio et al., 2012). The intermolecular interaction and rigidity of PLGA might be stronger, hence increased the T_g of PLGA. The PLGA-NEMs with HPβCD also showed a T_g at 230 °C, which could be attributed to the glass transition of HPβCD (Fig. S3).

CLX raw material showed a melting point at 161 °C (onset point), the melting point of spray dried CLX nanoparticles decreased to 146 °C, which corresponds to the previously reported melting point for polymorphic form IV of CLX (Lu et al., 2006). The melting peak disappeared in the thermogram of CLX-NEMs after spray drying with HPβCD, which could be explained by the limited growth of the nanoparticles in the presence of HPβCD. Another explanation could be the coating of HPβCD on the surface of CLX nanoparticles, which might result in surface amorphization of the nanoparticles (Kayaert and Van den Mooter, 2012).

3.3. Spectroscopic analysis of the spray dried NEMs

The thermal analysis results (Fig. 4) also indicated similar solid form changes of the PLGA and CLX after spray drying. All samples containing PLGA showed obvious glass transition on the thermograms, which indicated the amorphous state of PLGA-NEMs. The glass transition (T_g) of PLGA after spray drying (PLGANP) showed a slight increase from 44 to 47 °C compared with the PLGA raw material, the possible reason might be that PLGA was dissolved in a good solvent i.e. acetonitrile, and resulted in PLGA powder with high density after spray drying (O’Addio et al., 2012). The intermolecular interaction and rigidity of PLGA might be stronger, hence increased the T_g of PLGA. The PLGA-NEMs with HPβCD also showed a T_g at 230 °C, which could be attributed to the glass transition of HPβCD (Fig. S3).

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FTIR and Raman spectroscopy were used in this study to analyze the
impact of spray drying on the solid state of the samples and the possible interactions between nanoparticles and the stabilizers. It could be observed on the FTIR spectra that the PLGA raw material had an absorption peak at 1747 cm\(^{-1}\), which could be assigned to the carbonyl functional group. This peak was shifted to 1754 cm\(^{-1}\) after spray drying of the nanoparticles even without stabilizer, which is in agreement with previously reported results (Pietra et al., 2017; Elsaid Ali et al., 2013). The carbonyl peak was further shifted to 1759 cm\(^{-1}\) after spray drying with HPβCD (Fig. 5). The reason for the shift could be linked to the presence of HPβCD, which potentially disrupted the self-associations of PLGA molecules (Li et al., 2019; Yusop et al., 2015). This could be verified by PLGA NEMs containing different stabilizers and different ratios of stabilizers (Fig. S4).

When the ratio between stabilizer and PLGA was 4:1 (w/w), all PLGA NEMs with different stabilizers showed same absorption peak at 1759 cm\(^{-1}\). With the increase of stabilizer: PLGA ratio (PVP was used as the stabilizer in this case) from 1:1 to 4:1 (w/w) in the NEMs, the absorption peaks shifted from 1753 cm\(^{-1}\) to 1759 cm\(^{-1}\), indicating the stronger disruption effect for PLGA self-association with higher ratios of stabilizers. It was observed on the Raman spectra that the C–O stretching bond of PLGA ester groups displayed vibration peak at 1769 cm\(^{-1}\) (Sanna et al., 2012; Van Apeldoorn, 2005), and this peak was slightly shifted to 1763 cm\(^{-1}\) after spray drying with HPβCD, which also confirmed the disruption of self-associations among PLGA molecules. A

**Fig. 4.** Thermograms of raw materials (PLGA/CLX), spray dried nanoparticles without HPβCD (PLGANP/CLXNP) and spray dried nanoparticles with HPβCD as stabilizer (PLGA-NEM/CLX-NEM).

**Fig. 5.** FTIR spectra and Raman spectra of raw materials (PLGA/CLX), spray dried nanoparticles without HPβCD (PLGANP/CLXNP) and spray dried nanoparticles with HPβCD as excipient (PLGA-NEM/CLX-NEM).
similar Raman shift has been reported in previous studies with electrospinning PLGA (Shin et al., 2018). The prevention of PLGA self-associations by HPβCD in PLGA NEMs could contribute to the superior redispersion of PLGA nanoparticles by reduction of the interactions between PLGA molecules.

On the FTIR spectrum of CLX samples, the shift of the stretching vibration of C-F bond from 1229 cm\(^{-1}\) to 1237 cm\(^{-1}\) and the shift of the asymmetric S=O stretching bond of CLX from 1346 cm\(^{-1}\) to 1341 cm\(^{-1}\) were used as evidence to show the solid state change of crystalline CLX to amorphous CLX in the previous reports (Andrews et al., 2010; Hyun et al., 2019; Gupta and Bansal, 2005). However, the peak shift here might be caused by the use of PVPVA, which disrupted the interactions among CLX nanoparticles. With the addition of HPβCD, the peak caused by S=O stretching was further shifted to 1333 cm\(^{-1}\), because the addition of HPβCD further reduced the interactions among CLX nanoparticles (Wan, 2014). The disruption of the interactions among CLX nanoparticles was also evident from the Raman shifts of the phenyl ring bending peak from 809 cm\(^{-1}\) to 798 cm\(^{-1}\) (Edinger et al., 2018; Vijayakumar et al., 2016), and the shift of the O–H bending peak from 1613 cm\(^{-1}\) to 1618 cm\(^{-1}\) (Xie and Taylor, 2016; Dave et al., 2019).

### 3.4. Tabletability and compressibility of the compacts with nanoparticles

The tabletability and compressibility of the compacts with nanoparticles are illustrated in Fig. 6. Tabletability is important for evaluating whether a compact has enough tensile strength at the applied compaction pressure, and normally a higher compaction pressure results in a stronger compact (Patel et al., 2011). Typically, 1 to 2 MPa of tensile strength is needed in order to keep the compacts intact for further post-processing and handling (Bowles et al., 2018). The compacts compressed from PLGA NEMs or CLX NEMs with HPβCD in this study both showed a tensile strength greater than 1 MPa at 140 MPa compaction pressure, which was sufficient for compressing a strong compact even without using any fillers. It is worth noticing that the tensile strength of compacts with PLGA nanoparticles was higher than the compacts with CLX nanoparticles when compressed with the same fillers under the same compaction pressure. This is explained by the plastic properties of PLGA while CLX had more fragmentating properties (Wang et al., 2010). In this study, we only used compaction pressures up to 140 MPa, and it resulted the tensile strength of the compacts higher than 1 MPa, which would guarantee the strength of the compacts. The addition of SSG as the filler in the compact did not improve the tabletability of the NEMs.
notably while SMCC improved tabletability largely for both compacts containing PLGA nanoparticles or CLX nanoparticles. This was because SMCC has high plasticity (Thoorens et al., 2014) while SSG possesses high elasticity and decreases interparticulate bonding (Patel et al., 2016), these different characteristics of the fillers resulted in different compactibility of the compacts. Compacts with SMCC showed higher compactibility than compacts with SSG as filler. The fillers i.e. SMCC and SSG did not improve the compressibility of the powders notably except at low compaction pressure (35 MPa), where the compacts with SSG showed a higher solid fraction compared with compacts without a filler or with SMCC as filler. In conclusion, the compacts compressed from spray dried PLGA NEMs or CLX NEMs could have sufficient tabletability even without using fillers, and the addition of SMCC could largely improve the tabletability of the powders.

3.5. Redispersibility of nanoparticles from the compacts

The redispersibility of the nanoparticles is crucial for the performance of the compacts with nanoparticles because the benefits of drug delivery such as targeted delivery, enhanced dissolution rate and improved bioavailability rely on the characteristics of the individual nanoparticles. The size of original PLGA nanoparticles is ca. 200 nm. It could be observed that the redispersed PLGA nanoparticles from spray dried NEMs and the compacts had similar size and \( \text{PDI} \) compared with the original nanoparticles (Fig. 7). The compaction pressure did not show any obvious impact on the size and \( \text{PDI} \) of the redispersed PLGA nanoparticles because of the plastic properties of PLGA.

Unlike PLGA nanoparticles, the redispersion of CLX nanoparticles from NEMs and the compacts were more obviously affected by compaction and the fillers used in the compacts. The size of the original CLX nanoparticles was around 160 nm and the \( \text{PDI} \) was around 0.04. However, the size of redispersed CLX nanoparticles from CLX NEMs was greater than 1000 nm, and obvious aggregates could be seen from the redispersed suspension.

Although it is possible to spray dry the nanosuspensions without using excipients, which lead to the formation of microparticles (a type of NEMs without matrix), the redispersibility of the nanoparticles from NEMs would be a challenge (Wang et al., 2017). It has been reported that the aggregation of nanoparticles depends on the molecular interaction as well as the hydrophobicity of the nanoparticles (Hou et al., 2017). The hydrophilic excipient, HP\( \beta \)CD, could form amorphous matrix around the nanoparticles during spray drying process (Vega et al., 2012), hence decreasing the interactions between nanoparticles. In addition, HP\( \beta \)CD could increase the wettability of the nanoparticles. As a result, the aggregation of the nanoparticles was decreased. However, since CLX (log P value 3.5) has higher hydrophobicity compared to PLGA (log P value 2.6) (D’Addio et al., 2012; Van Eerdenbrugh et al., 2008), more HP\( \beta \)CD is needed to achieve the same wettability with spray dried PLGA powders. Another explanation might be the different aggregation kinetics influenced by surface charge, CLX nanoparticles has zeta potential around 8 mV while for PLGA nanoparticles, the surface charge is around –44 mV (data not shown).

Interestingly, after direct compaction of the CLX NEMs into compacts, the redispersed CLX nanoparticles were smaller compared with those redispersed from spray dried NEMs powders. This might be caused by the fragmentation of the nanoparticle aggregates upon compaction. With the addition of fillers i.e. SMCC and SSG, the size of redispersed CLX nanoparticles was larger than nanoparticles redispersed from compacts without fillers. The redispersed nanoparticles from CLXSSG-compact were substantially larger than those redispersed from CLXSM-compact.
compact. This is explained by the plastic properties of SMCC and the resulting particle deformation upon compaction while the more elastic SSG had no deformation (Skelbek-Pedersen et al., 2019). Therefore, SSG is believed to prevent the nanoparticles from fragmenting compared with SMCC. It has to be mentioned that although HPβCD accounts for high amount in spray dried particles, however, HPβCD is a plastic material (Suihko et al., 2000), the cushioning effect of HPβCD is not as strong as the elastic material SSG. The redispersion results indicated that the fillers in the compacts acted as the cushioning agents, which would decrease the impact of compaction stress on the particles (Li et al., 2016). Future studies should investigate the use of fragmenting and non-fragmenting excipients to support this hypothesis.

3.6. Dissolution enhancement of CLX compacts

The main purpose of including drug nanoparticles in this study was for their dissolution enhancing application for poorly soluble drugs. The dissolution profile of CLX compacts was assessed to investigate whether the compaction process compromises the dissolution rate of the drug. It was observed that the CLX was released slowly from the physical mixture compacts (mixture of CLX crystals and filler) regardless of using SMCC or SSG as the filler, and only 10% of cumulative drug release was achieved in 580 min (Fig. 8). Compared with the compacts made of the physical mixture of CLX and filler, around 4.5-fold higher CLX was released from the compacts compressed from NEMs without fillers during the same time (580 min). The CLXSSG compact released 7-fold higher CLX compared with the physical mixture compact PM CLXSSG in 60 min. The CLXSM compact released 5-fold higher CLX in 60 min than its equivalent physical mixture PM CLXSM compact. The release of CLX from compacts both in short term and long term are enhanced, which indicates the nanoparticles did not precipitate during dissolution. Therefore, it can be concluded that the preparation of CLX nanoparticles enhanced the dissolution of the drug and the dissolution of CLX was still faster after compression of the nanoparticles into compacts. Especially, when fillers were used in the compacts, the dissolution of CLX was even faster than the compacts compressed from CLX NEMs without fillers. Compared with SMCC, SSG showed stronger dissolution enhancement for CLX. This can be explained by the high swelling capacity of SSG (Gohel et al., 2007), as observed from the fast disintegration of the CLXSSG-compacts during the dissolution studies compared with CLXSM-compacts. Another reason for the higher CLX dissolution rate observed may be the change of CLX polymorph, as reported that the new polymorphic form IV of CLX has a higher dissolution rate compared to the stable form III (Lu et al., 2006).

CLX nanoparticle accounted for 17% (w/w) in the compacts (CLXSSG-compact and CLXSM-compact) compacted together with SMCC or SSG. In the CLX-NEM compacts, CLX has a composition of 33% (w/w). The drug loading of CLX nanoparticles in the compacts are still relatively low compared to marketed drugs using CLX crystalline drug (Celebrex®), however, the preparation of CLX nanocrystals in the compacts has potential to improve the dissolution of the drug.

It needs to be mentioned that the PLGA nanoparticles are also used as model nanoparticles in this study, however, the PLGA nanoparticles were not loaded with APIs. Although the composition of PLGA nanoparticles in the compacts are 17% (compressed with SMCC/SSG) or 33% (compressed without SMCC/SSG), there might be a problem of low API loading when the nanoparticles are loaded with drugs. Therefore, the application of the compacts with polymeric nanoparticles might have limited use for loading of low-dose drugs such as vincristine (Song et al., 2009). However, the compacts could have broader applications with increasing studies on stabilizers for dispersible compacts compressed with nanoparticles.

4. Conclusion

PLGA nanoparticle suspensions and CLX nanoparticle suspensions were used as models for nanoparticle systems and transformed into dry powders by spray drying, which was followed by transformation into compacts by direct compression. Our study showed that HPβCD could effectively prevent nanoparticles from aggregation during spray drying due to the disruption of the intermolecular interactions of PLGA or CLX. The solid form transformation of CLX was observed after the preparation of CLX nanoparticles and engineering of the nanoparticles into NEMs. We have to acknowledge that although this polymorphic form (form IV) has higher bioavailability than the original form of CLX (Lu et al., 2006), it might experience instability issues. Therefore, other excipients have to be studied for obtaining stable CLX nanoparticles without changing the polymorphic form. The NEMs could be directly compressed into compacts with sufficient tensile strength for further handling and processing. The addition of SMCC as filler improved the tableiability of the NEMs but not the compressibility. CLX nanoparticles were more prone to aggregation than PLGA nanoparticles upon spray drying and compression into compacts, even with higher amounts of stabilizers. PLGA nanoparticles could be completely reconstituted into nanoparticles from NEMs or compacts. The dissolution rate of CLX from the compacts was largely improved although with an increased size of the redispersed

![Fig. 8. Dissolution profile of CLX compacts compacted from NEMs without filler (CLXNEM-compact), NEMs with SMCC as filler (CLXSM-compact), NEMs with SSG as filler (CLXSSG-compact) and physical mixture with SMCC (PM CLXSM-compact) and SSG (PM CLXSSG-compact).](image-url)
nanoparticles. Fillers could be used as cushioning excipients in compacts in order to alleviate the compaction on the particles. It was concluded that nanoparticles can be compressed into compacts without significantly compromising the merit of nanoparticles or the functional properties of the compact. The transformation of nanoparticles into compacts could be a feasible strategy to transform the nanoparticles into a solid form to improve physical stability of nanoparticles as well as a solid oral dosage form for increased performance in the digestive tract.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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