Pharmaceutical nanoparticle isolation using CO₂-assisted dynamic bed coating

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A R T I C L E   I N F O

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A B S T R A C T

Poor solubility of new chemical entities (NCEs) is a major bottleneck in the pharmaceutical industry which typically leads to poor drug bioavailability and efficacy. Nanotechnologies offer an interesting route to improve the apparent solubility and dissolution rate of pharmaceutical drugs, and processes such as nano-spray drying and supercritical CO₂-assisted spray drying (SASD) provide a route to engineer and produce solid drug nanoparticles. However, dried nanoparticles often show poor rheological properties (e.g. flowability, tabletability) and their isolation using these methods is typically inefficient and leads to poor collection yields. The work presented herein demonstrates a novel production and isolation method for drug nanoparticles using a ‘top spray dynamic bed coating’ process, which uses CO₂ spray as the fluidizing gas. Nanoparticles of three BCS class II Active Pharmaceutical Ingredients (APIs), namely carbamazepine (CBZ), ketoprofen (KET) and risperidone (RIS), were produced and successfully coated onto micron-sized microcrystalline cellulose (MCC) particles. The size distribution of the API nanoparticles was in the range of 90–490 nm. The stable forms of CBZ (form III), KET (form I), and the metastable form of RIS (form B) were produced and coated onto MCC carrier microparticles. All the isolated solids presented optimal rheological properties along with a 2–6 fold improvement in the dissolution rate of the corresponding APIs. Hence, the ‘top spray dynamic bed coater’ developed in this work demonstrates to be an efficient approach to produce and coat API nanoparticles onto carrier particles with optimal rheological properties and improved dissolution.

1. Introduction

The emerging use of combinatorial chemistry in drug development has resulted in new drug candidates with high lipophilicity, high molecular weight and low water solubility. The majority of the failures in new drug development have been attributed to low water solubility of the drugs which leads to poor bioavailability and results in sub-optimal drug delivery/efficacy (Kalepu and Nekkanti, 2015). Nearly 40% of the top 200 oral drugs marketed in the USA and Europe, and 90% of the new chemical entities which are in the drug development pipeline in the pharmaceutical industry are poorly water soluble (Tan et al., 2017). Thus, low solubility of drugs at the site of administration leads to low quantity of available diffusion, leading to insufficient drug concentration at the site of action and in-vivo failure (Siepmann and Siepmann, 2013). Modified formulation strategies have been gaining traction in the pharmaceutical arena due to their ability to improve the dissolution of BCS (Biopharmaceutical Classification System) Class II and IV drugs. Some of the available drug delivery technologies with a potential to circumvent the solubility, dissolution rate and bioavailability of the poorly soluble drug include amorphous solid dispersions, crystal engineering, inclusion complexes, lipid based formulations and nanoparticles (Loftsson and Brewster, 2010; Alam et al., 2012; Müllertz et al., 2010; Rabinow, 2004).

In the recent years, nanosizing has emerged as an important drug delivery platform approach for the commercial development of the poorly soluble pharmaceutical drugs. Nanoparticles can be produced either by top-down or bottom-up approaches. Top-down methods involve the breakage of large particles into smaller ones, which is typically achieved by milling or high pressure homogenization. Both of these top down techniques have been meticulously studied and discussed in the literature by Müller in his reviews (Keck and Müller, 2006; Shegokar and Müller, 2010; Müller et al., 2001), and by other authors (Hanafy et al., 2007; Jia et al., 2003; Jinno et al., 2006; Onoue et al., 2013). In contrast to top-down methods, bottom-up methods generate nanoparticles by building them from drug molecules in solution, which typically is achieved by controlled precipitation (antisolvent
precipitation, sonoprecipitation etc.) and solvent removal (spray-drying, electrospraying etc.) techniques (Chan and Kwok, 2011). Generally, the production of nanoparticles using top-down techniques requires high energy, which generally leads to contamination if a milling method is applied. While the bottom-up approach possess advantages such as low energy requirements and lower cost, these methods typically use organic solvents which are difficult to remove from the product (Miyazaki et al., 2016).

Nanosizing formulation techniques generate drug nanocrystals with a mean particle size between 1 and 1000 nm. Nanoparticles vary distinctly in their properties from micronized drug particles due to their small particles size. Similarly to other colloidal systems, drug nanocrystals tend to reduce their energy state by forming larger agglomerates or crystal growth (Möschwitzer, 2013). Particle agglomeration, recrystallisation and amorphization are the main instability factor for the drug nanoparticles. Thus, they are often stabilized with surfactants, stabilizers or combinations thereof (Gigliobianco et al., 2018). These instability factors often lead to inefficient formulation strategies for the drug products and impact significantly their rheological properties due to poor flowability and compressibility.

Carbon dioxide (CO₂) is being used in the pharmaceutical production as a replacement to organic solvents because it is abundant, nontoxic, inexpensive, and suitable for development of environmentally friendly processes (Long et al., 2019a, 2019b). Supercritical CO₂ (scCO₂) has attracted attention of the pharmaceutical researchers in the last few decades due to its ability to manufacture fine drug particles in amorphous or crystalline form (Long et al., 2019b; Matos et al., 2020; Li et al., 2017). There are various particle engineering techniques which use scCO₂ either as a solvent (e.g. RESS, RESOLV, RESSAS) (Leeke et al., 2014; Sun et al., 2005; Türk, 2009), an antisolvent (e.g. SAS, GAS) (Long et al., 2019a; Gallagher et al., 1989; Marr and Gamse, 2000), or an atomization enhancer (e.g. SASD, SAA, PGSS) (Long et al., 2019b; Reverchon et al., 2003; Bahrami and Ranjbarian, 2007). Compared to most supercritical CO₂-based techniques, SASD is further favored for the production of spray dried micro- and nanoparticles, as it restrains the high-pressure into a small mixing chamber/nozzle and has the ability to operate in continuous mode, which is the new stepping stone in the pharmaceutical industry. The main benefits of the SASD process is as follows (Arpagaus et al., 2017; Padrela et al., 2018):

- Conversion of liquid to powder in one step
- Nano/microparticle generation at atmospheric pressure
- Control of particle size and solid form (amorphous/crystalline form)
- Scale-up capability
- Process simplicity with ease of operation

The SAS process has been used in combination with a fluidized bed to coat drug nanoparticles onto micron-sized carrier particles by Li et al., (Li et al., 2017). Naringin was dissolved in either methanol, ethanol or acetone, and sprayed onto fluidized carrier particles under high pressure. This resulted in amorphous naringin nanoparticles (100–200 nm) coated onto fluidized carrier particles with a drug loading of 2.5% and processing yield between 44 and 99%. Since the process was under high pressure, scalability would be an issue thereby restricting its potential use in an industrial environment. Leeke et al., reported on the combination of the RESS process with a fluidized bed to coat organic molecules.
onto microcrystalline cellulose (MCC) particles (Leeke et al., 2014). These authors successfully coated 30 nm nanoparticles onto MCC with a loading of < 1% and processing yield between 14 and 74%. Low loading is related to the typically low solubility of organic molecule in scCO\textsubscript{2} and this is one of the main reasons that limits the applicability of RESS for pharmaceutical production. Hence, there is a need for new processes that provide high processing yields with high drug loadings, and that are able to operate at ambient pressure.

The work presented in this paper shows a novel top spray dynamic bed coating method to capture/coat API nanoparticles onto micron-sized carrier particles with minimum use of stabilizers. Three BCS class II APIs, namely carbamazepine (CBZ), ketoprofen (KET), and risperidone (RIS) were selected as model systems for the proof of concept of this method, while microcrystalline cellulose (MCC, PH102) was used as carrier material. All the experiments were performed at the same API concentration, temperature, pressure, solution and CO\textsubscript{2} flow rate for an efficient comparison of the data. Two drug loadings of 10% and 20% were used, as previous studies have only reported drug loadings of < 5%. These drug loadings are based on the fact that the API loading in most of the direct compression tablet does not exceed 30% because of the poor processability (Chen et al., 2019; Jivraj, Martini, and Thomson, 2000). The API-MCC composite samples produced were analyzed to determine the exact API loading, processing yield, nanoparticle size and solid form. Further the isolated solids were assessed for their flowability properties and the improvement in the dissolution rate of the APIs, while the tablets prepared of the API-MCC composite were tested for tabletability, compressibility and compactability.

2. Experimental section

2.1. Materials

Methanol (MeOH, > 99.9%) and sodium dodecyl sulfate (SDS, > 99.9% pure) were supplied by Sigma-Aldrich and used as-received. Carbamazepine (CBZ, > 98% pure, CCDC CBMZPN01) and Risperidone (RIS, > 98% pure, CCDC WASTEP) were supplied by Kemprotec and used as-received. Ketoprofen (KET, > 98% pure, CCDC KEMRUP) were kindly offered by Clarochem and used as-received. Microcrystalline cellulose (MCC) (MW: 36000 g/mol) was kindly offered by FMC International and used as-received. Liquid carbon dioxide (99.98%) was supplied by BOC (Ireland). Fig. 1 provides the molecular structures of the carrier particles (MCC), the solvent (MeOH) and the APIs (CBZ, KET and RIS) used in this study.

2.2. API solution preparation

For the production and isolation of API nanoparticles using a top spray dynamic bed coating process, CBZ, KET and RIS were dissolved in 40 mL of methanol (50 mg/mL) using an ultrasonic bath until a clear solution is obtained. In the case of CBZ, 10% w/w (5 mg/mL) of the additive SDS was added to the CBZ methanol solution to favour the formation of the stable polymorphic form III of CBZ (Padrela et al., 2017; Long et al., 2019b). The solutions were then filtered using 0.2 µm nylon syringe filter (Whatman Inc., Florham Park, NJ) to remove any undisolved impurity.

2.3. Production and isolation of API nanoparticles using top spray dynamic bed coating

Fig. 2 presents a schematic of the top spray dynamic bed coating process with an enlarged view of the drying chamber consisting of co-axial nozzle at the top, carrier particle holder in the middle and CO\textsubscript{2} outlet at the bottom part of the chamber.
During the experiments CO₂ was compressed to 100 bar using a SFE process Dose HPP 400-C pump. The nozzle was maintained at 50°C by using heating resistors in close proximity to the nozzle. Each API methanol solution was pumped at a flow rate of 0.4 mL/min to the high-pressure nozzle using an Agilent technologies 1260 Infinity II pump, where it was mixed with the supercritical CO₂. After the solution was passed through the nozzle, the supercritical CO₂ was depressurised and any residual solvent was evaporated during the spray-drying step passing through the vent at the bottom of the chamber. The process variables used in this study were established based on the previous study from the group by Barry et al., (Long et al., 2019b). They discovered that using 10 wt% SDS in CBZ solution results in the controlled nucleation of the stable form (Form III) of carbamazepine. Further, it was reported that carbamazepine methanol solutions with a concentration of 50 mg/mL resulted in the formation of crystalline carbamazepine using the SASD method, as compared to 17 mg/mL solution concentrations which resulted in the formation of amorphous carbamazepine. In addition, carbamazepine Form III was obtained when the carbamazepine solution flow rate of 0.4 mL/min in comparison to 0.1 mL/min solution flow rate resulting in the formation of mixture of polymorphs. Those authors also suggested that CO₂ pressure did not greatly impact the polymorphic outcome. Therefore, we have used similar processing conditions for the experimental runs performed in this study i.e. API concentration of 50 mg/mL, API flow rate of 0.4 mL/min, CO₂ pressure of 100 bar and SDS concentration of 10 wt% in the case of carbamazepine. Further, the authors also performed a preliminary Design of Experiments (DOE) study to fix the API loading to 10% and 20%.

During the API nanoparticle isolation step, the MCC particles were placed on the partially open mesh and were fluidized using CO₂ and/or N₂ (four bar) nitrogen (also acted as drying gases). The nanoparticle spraying process was initiated only after the fluidization of the MCC particles. Upon completion of spraying, the CO₂ flow was stopped while N₂ flow was continued for another 15 min to dry any residual solvent. The amount of MCC was adjusted to achieve 10% (18 g of MCC) and 20% (8 g of MCC) loading of API nanoparticles onto the MCC carrier particles. Each experiment was performed in triplicate to ensure the reproducibility of the process. The samples were harvested and stored in a desiccator prior to characterization to prevent exposure to humidity and minimize polymorphic conversions over time. The API loading is calculated according to the Eq. (1).

\[
\text{API loading} (\% /w) = \frac{(\text{mass of API sprayed})}{(\text{mass of API sprayed}) + (\text{mass of excipient})} \times 100
\]

2.4. Solid state characterisation of the API-MCC composites

2.4.1. API solid-state form determination

The solid state/polymorphic form of each API in the isolated API-MCC composite solid particles was determined using Powder X-ray Diffraction (PXRD) technique. Diffractograms were recorded on a PANalytical Empyrean diffractometer using a Cu radiation source (\(\lambda = 1.541 \text{ nm}\)) at 40 mA and 40 kV. Scans were performed between 5 and 35°2θ at a scan rate of 0.013°/20/min.

2.4.2. API nanocrystal habit determination

The habit of the isolated API-MCC composite solid particles was examined using scanning electron microscopy (SEM), Hitachi SU-70 system operating at 10 kV. Samples were mounted onto aluminum stubs with double-sided carbon tape. Samples were gold coated (S150B, Edward) and the surface appearances of the isolated API-MCC composite solids were compared.

2.4.3. Yield calculation

Processing yield was determined using Eq. (2).

\[
\text{Yield} = \frac{(\text{mass of API coated onto MCC})}{(\text{mass of API sprayed})} \times 100
\]

The amount of API coated onto MCC was determined by dissolving a pre-weighed amount of API-MCC composite in 1 L of deionised water. The amount of API-MCC composite particles was determined based on the API loading, so that the final solution concentration was 20 mg/mL. The solution was stirred at 400 rpm for 12 hr in a water bath maintained at a constant temperature of 37 ± 0.5°C. An aliquot (1 mL of the solution) was drawn using a syringe and filtered using 0.2 µm Nylon syringe filter. Both the syringe and the filter were heated at 50°C above the water bath temperature to avoid API precipitation. The aliquot was analysed using UV spectrophotometer at absorption maximum of 285 nm for CBZ, 276.5 nm for RIS and 216 nm for KET. The solution concentration was then determined using a calibration plot of the API determined at the respective wavelength, within a concentration range of 0.5 mg/L to 40 mg/L. The API concentration was then converted to the amount of API present in API-MCC composite, which then was used to determine the processing yield for the batch. A minimum of three samples were drawn from one batch of API-MCC composites to access the content homogeneity as well as reproducibility of the results.

2.4.4. Particle size distribution analysis of API nanoparticles

The size of the API nanoparticles attached onto MCC particles was measured from the respective SEM micrographs using the ‘measuring’ tool of ‘Adobe Acrobat Reader DC’. A minimum of 150 nanoparticles were measured for each sample. The average nanoparticle size and standard deviation were determined by averaging all the measurements and calculating standard deviations, respectively.

2.4.5. True density measurement

True density of the samples was measured at ambient temperature using the Accupyc II gas displacement pycnometry system (Micrometrics®, Nocross, GA, USA) based on USP 699 standard procedure. Helium was purged into the sample chamber to determine its volume. True density is the mass of a substance divided by its volume, excluding open and closed pores.

2.4.6. Precompression studies of the API-MCC composites

Prior to the compression of API-MCC composites into tablets, the flow properties of the composites were assessed to check its suitability for compression. In order to access the flow properties of API-MCC composites, the compressibility index and Hausner’s ratios were adopted. The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and the tapped volume of a powder (Luner et al., 2001; Aulton, 1988). The compressibility index and the Hausner ratio are calculated according to Eq. (3) and Eq. (4) respectively.

\[
\text{Compressibility Index} = 1 - \frac{V_0 - V_t}{V_0}
\]

\[
\text{Hausner ratio} = \frac{V_0}{V_t}
\]

A Freeman Technology FT4 Rheometer was used to calculate the compressibility index of API-MCC composite powder. The compressibility measurement was performed by applying an increasing level of compression force with a vented piston to a conditioned powder and measuring the change in volume as a function of applied load. The Vented Piston ensures that air trapped within the powder is able to readily escape, allowing for precise definition of compressibility which is expressed as a percentage change in volume for a given applied normal stress. The experiments and calculations were performed in triplicate.
2.4.7. Tableting of API-MCC composite

A Gamlen R-series compaction simulator (Gamlen tableting limited, UK) was used to compact the API-MCC composite particles. Samples of \( \sim 100 \) mg were tableted and 

\[
\sigma = \frac{2F}{\pi Dt}
\]  

(5)

where, \( \sigma \) is the tensile strength of the tablets (MPa), \( F \) is the tablet diameter in (mm) and \( t \) is the thickness (mm) of the tablet which were measured at once using a PharmaTest hardness tester. The diametral breaking force was also measured using the PharmaTest hardness tester.

2.4.7.2. Tablet porosity. Tablet porosity was calculated using Eq. (6):

\[
\text{Tablet porosity} = 1 - \frac{\rho_{\text{app}}}{\rho_{\text{true}}} 
\]  

(6)

where, \( \rho_{\text{app}} \) is apparent density and \( \rho_{\text{true}} \) is the true density (g/cm\(^3\)).

2.4.7.3. Tabletability. The ability of the material to form compacts with a certain tensile strength under the applied compaction pressure is called tabletability. It is usually represented using a graph of tensile strength as a function of compaction pressure. The linear correlation between tensile strength and compaction pressure of the tablet proposed by Newton et al., (Newton et al., 1971) is as follows (Eq. (7)):

\[
\sigma_t = C_p P + b
\]  

(7)

where, \( C_p \) is the tabletability parameter, \( P \) is the compaction pressure and \( b \) is a constant.

2.4.7.4. Compactability. The graph of tensile strength as a function of tablet porosity helps to understand the compactability of the material. A mathematical representation of compactability is provided by the Ryshkewitch-Duckworth equation (Eq. (8)) (Ryshkewitch, 1953).

\[
\sigma_t = \sigma_o e^{-3P}
\]  

(8)

where, \( \sigma_t \) and \( \sigma_o \) are tablets tensile strength (MPa) and tablet tensile strength at zero porosity (MPa), respectively. \( P \) is tablet porosity and \( b \) is an empirical constant representing bonding capacity. Steendam and Lerk explained that higher \( b \) value represents stronger bonding capacity of primary particles (Steendam and Lerk, 1998).

2.4.7.5. Compressibility. Compressibility of the API nanoparticles coated onto MCC particles was assessed using Heckel model. Heckel model explores the porosity reduction upon applied compression pressure according to Eq. (9).

\[
-\ln e = \ln \left( \frac{1}{1 - D} \right) = kP + A
\]  

(9)

where, \( e \) is tablet density, \( D \) is the relative density of the tablets, \( k \) is the Heckel coefficient, \( P \) is the applied compression pressure and \( A \) is the intercept. Reciprocal of the Heckle coefficient results in yield pressure - tensile strength at zero porosity (MPa), respectively.

| Table I | Summary of the average particle size (nm), polymorphic form, and yields (%) achieved from the nanoparticle isolation experiments performed using top-spray dynamic bed coating process for carbamazepine (CBZ), risperidone (RIS) and ketoprofen (KET) using microcrystalline cellulose (MCC) as carrier particles. SD: standard deviation.

| API | Run | Average particle size (nm) ± SD | Polymorphism | Yield achieved (%) |
|-----|-----|------------------------------|-------------|-------------------|
| CBZ | R1  | 180 ± 52                     | FIII        | 75 ± 0.7          |
|     | R2  | 196 ± 89                     | FIII        | 61 ± 1.3          |
|     | R3  | 90 ± 28                      | FIII        | 79 ± 0.7          |
| RIS | R1  | 360 ± 90                     | Form B      | 76 ± 2.9          |
|     | R2  | 316 ± 68                     | Form B      | 67 ± 6.0          |
|     | R3  | 345 ± 93                     | Form B      | 62 ± 10           |
| KET | R1  | 490 ± 160                    | FI          | 58 ± 3.7          |
|     | R2  | 380 ± 70                     | FI          | 62 ± 1.7          |
|     | R3  | 380 ± 75                     | FI          | 89 ± 2.6          |

2.4.8. In vitro drug release studies

The dissolution of powder samples was performed under sink conditions with a maximum CBZ solution concentration, \([\text{CBZ}]_{\text{max}}\) of 20 mg/L, KET solution concentration, \([\text{KET}]_{\text{max}}\) of 15 mg/L, and RIS solution concentration, \([\text{RIS}]_{\text{max}}\) of 15 mg/L. Dissolution was carried out using a PHARMATEST PTWS 120D dissolution test system, USP type II (paddle) apparatus. Dissolutions were performed in 1000 mL deionised water at \(37 ± 1^\circ\text{C}\) with a paddle rotation of 100 rpm. One mL aliquots were withdrawn at predetermined time intervals (1, 3, 5, 10, 15, 30, 45 and 60 min) and filtered by Whatman Nylon 13 mm filters of 0.2 μm pore size before being analysed by UV spectrophotometry. The API absorption maximum (as mentioned in Section 2.4.3) was used to quantify the amount of API dissolved. Further, dissolution curve fitting was achieved using Korsmeyer-Peppas model. Korsmeyer and Peppas put forth a simple relationship that describes the drug release from a polymeric system and type of dissolution (Eq. (10)).

\[
F = Kt^n
\]  

(10)

where, \( K \) is Korsmeyer release rate constant and \( n \) is the drug release exponent.

3. Results and discussion

Nanoparticles of carbamazepine (CBZ), risperidone (RIS) and ketoprofen (KET) were successfully produced and coated onto micron-sized MCC particles using top spray dynamic bed coating process. Table I presents the processing yields achieved for the experiments where 10% and 20% loadings of each API (e.g. CBZ, RIS, KET) onto MCC were used. For each API, experiments were performed in triplicate for each loading. Processing yields achieved for CBZ and RIS were in the range of 61–76%, and for KET in the range of 49–89%. The processing
yields achieved in this work were 10–20 fold higher than the yields typically achieved using nano spray dryers equipped with fluidized bed coater (Li et al., 2017; Matos et al., 2020, 2018) or wurster coater (Leeke et al., 2014), where the yields have been reported to be between 1% and 4%.

Fig. 3 presents the PXRD patterns of the isolated API-MCC composite samples at different drug loadings. The stable forms of CBZ (Form III) and KET (Form I) were obtained at both 10% and 20% loadings, whereas the metastable form of RIS (Form B) was obtained. Three different batches of each API at each loading generated similar PXRD results confirming the robustness and reproducibility of the top spray dynamic bed coating process. The intensity of the PXRD peaks is small for both batches of each API at each loading, particularly for 10% loading. This is because for 10% loading samples the yield was around 50–60%, therefore the real loading is around 5–6% (10% of the yield achieved). This allowed the authors to work at a lower detection limit of the PXRD instrument. Also, since the major fraction of all the samples produced corresponded to MCC, the broad peaks of MCC in the PXRD patterns are clearly visible for each sample.

Fig. 4 presents the SEM micrographs of the solids isolated after the experiments at 10% and 20% loadings. A summary of the average particle size distributions along with standard deviations is also reported in Table 1. The SEM micrographs in Fig. 4 confirm the uniform coating of API nanoparticles onto the micron-sized MCC carrier particles. The average size of CBZ nanoparticles was in the range of 90–200 nm, for RIS was 280–350 nm, and for KET was 300–500 nm. The process parameters such as pressure, temperature, solution concentration, CO2 flow rate and nozzle size were kept constant for each experiment, emphasising on the similar size and number of droplets formed during each experiment. Hence, the generation of nanoparticles was not only governed by the process parameters but also by the different nucleation and growth properties of the APIs. From the particle size results obtained it is evident that the KET is a fast-growing API, while CBZ is a slow-growing API and RIS is a moderately-growing API.

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms, in order to avoid high dose variation due to irregular feed and filling of tablet dies. Three flow measurements namely, the angle of response, compressibility index and Hausner’s ratio can be employed to assess the flowability of a powder (Fahmy and Kassem, 2006). In this work, the compressibility index and Hausner’s ratio was used to evaluate the flow properties of the API-MCC composites. The compressibility index has also been proposed as an indirect measure of bulk density, shape and size, surface area, moisture content and material cohesiveness and these can influence the compressibility index of a material (Brittain, 1995). Fig. 5 presents the powder compressibility index of the microcrystalline cellulose, 10% and 20% loaded API-MCC composite powder, repeated for three different batches. Considering the standard deviation of all powders, the compressibility index is similar at all applied stress. This signifies that the coating of API nanoparticles onto MCC particles retained the flow behavior of MCC (PH102) particles. Flowability of MCC PH102 is one of critical benchmark manufacturing parameters in the pharmaceutical industry (Chen et al., 2019).

The Hausner’s ratio and the compressibility index were calculated for the applied stress of 4 kPa. Powders presenting the compressibility index of up to 25 are considered of acceptable flow properties (Aulton, 1988; USP convention <> Powder Flow [Harmonization] USP 29/NF 24, 1174). The Hausner’s ratio is related to the inter-particle friction and the powders with low inter-particle friction presenting the Hausner’s ratio of up to 1.35 are considered of acceptable flow properties (Aulton, 1988; USP convention <> Powder Flow [Harmonization] USP 29/NF 24, 1174). Therefore all the powders including MCC (PH102), 10% and 20% loaded API-MCC composites exhibited acceptable flow properties, with an exception of 20% loaded CBZ-MCC composites which fall at the boundary of passable and poor flowing powders (in alignment with the data presented in Table 2 for compressibility index and Hausner’s ratio). Potentially this could be due to a large number of free CBZ nanoparticles in the CBZ-MCC composite, leading to an increase in compressibility index, Hausner’s ratio and poor flowability of the powder.

The mechanical strength of pharmaceutical tablets is a bottleneck tablet property, as it impacts the pharmacokinetic and pharmacodynamic behavior of the tablets (Michrafy et al., 2007; Wu et al., 2005). As mentioned in the introduction section, nanoparticles typically exhibit poor rheological properties. However, using the top spray dynamic bed coating process, the API nanoparticles presented optimal rheological properties. The mechanical strength of the tablets of the API-MCC
composites were examined by comparing their tabletability, compactability and compressibility profiles.

Tabletability is considered to be an ability of the powder to compress into a tablet with specific tensile strength. It is usually represented as a graph between tensile strength (MPa) versus compaction force (kN).

Fig. 6 presents the tabletability profile of the tablets compressed for 10% and 20% loadings of API-MCC composites. The tensile strength of all the samples linearly increased with an increase in compaction force. MCC exhibited the highest tensile strength at the compaction force of 5kN, while the tensile strength of each isolated API-MCC composite was
Table 2
Powder compressibility parameters, compressibility index (in %) and Hausner’s ratio for 10% and 20% API-MCC composite powder along with MCC (PH102) powder compressed at applied stress of 4 kPa; SD: standard deviation.

| Loading | Sample  | Powder compressibility |  
|--------|---------|------------------------|
|        |         | Average compressibility index (%) | Average Hausner’s ratio ± SD |
| 10%    | MCC     | 16.8 ± 1.1             | 1.2 ± 0.02 |
|        | CBZ     | 20.9 ± 2.8             | 1.3 ± 0.04 |
|        | RIS     | 13.5 ± 0.6             | 1.2 ± 0.01 |
|        | KET     | 10.8 ± 1.5             | 1.1 ± 0.02 |
| 20%    | CBZ     | 26.2 ± 2.9             | 1.4 ± 0.05 |
|        | RIS     | 19.3 ± 1.3             | 1.2 ± 0.02 |
|        | KET     | 15.6 ± 2.2             | 1.2 ± 0.03 |

nearly half of the MCC. MCC is an easily compressible material with excellent tensile strength that has been extensively studied and reported in the literature (Pudasaini et al., 2017). Though the tensile strength of the API-MCC composite are lower than that of MCC, it is still considered good as the tensile strength is above 2 MPa at high compression force of 4 kN and above. A tensile strength value of >2 MPa is an essential requirement of the tablets for acceptable manufacturability, quality and biopharmaceutical performance (Chen et al., 2019). The tabletability parameter for each isolated solid was obtained using a linear regression. The slope of each line is an indicative parameter of the tabletability (parameter for each isolated solid was obtained using a linear regression. The slope of each line is an indicative parameter of the tabletability (Table 3). MCC exhibited the highest value of $C_p$ which is 1.5, while the 10% and 20% API-MCC composite samples presented a value of $C_p$ close to 1.0, signifying slightly poor tabletability of API-MCC composite compared to MCC.

Fig. 7 presents a graph of the tensile strength of MCC and each API-MCC composite samples as a function of porosity, to assess the compactability of the 10% and 20% API-MCC composite samples. Compactability of a powder relates the powder plastic deformation and its ability to reduce volume under applied pressure. Further, Ryskewitch–Duckworth equation (Barralet et al., 2002) was used to analyse the compactability of all samples. The fitted parameters are presented in Table 3. The tensile strength at zero porosity ($\sigma_{t0}$) for all 10% and 20% loaded API-MCC composite samples is higher than that of MCC. The only outlier is the 10% loaded KET-MCC sample with a $\sigma_{t0}$ is 8.48, which could be potentially due to larger nanoparticle sizes agglomerated together, thereby introducing larger porosity to the system. Moreover, a higher $b$ (constant) value is an indication of bonding capacity, representing a stronger bonding between the primary particles (Steendam and Lerk, 1998). MCC presents the lowest $b$ value compared to the 10% and 20% API nanoparticles loaded MCC, corresponding to a lower tendency of the MCC particles to interact with each other. On the contrary, a uniform API nanoparticle coating onto MCC particles increases the cohesive interactions between the API-MCC particles leading to a higher $b$ Value. This data also supported by the SEM micrographs in Fig. 4 which show a uniform coverage of the API nanoparticles onto the MCC particles.

Fig. 8 presents the compressibility results of the 10% and 20% loaded API-MCC composites, showing the plot of $-\ln$(Porosity) as a function of compaction force. The compressibility was analyzed using the Heckel equation. The Heckel coefficient, $K$ (slope of the Heckel plot) and inverse value of yield pressure, $P_y$ are presented in Table 3. MCC presents good plasticity and high compressibility properties based on its high Heckel coefficient and low yield pressure. On the contrary, 10% loading samples exhibit the inverse behavior than of pure MCC due to their low Heckel coefficient and high yield pressure, thereby presenting poor plasticity and low compressibility properties. Whereas, 20% loading samples presented improved compressibility compared to 10% loading sample but not as efficient as pure MCC.

Fig. 9 presents the dissolution profile of each of the 10% and 20% API-MCC composites, showing the plot of drug release as a function of time. The dissolution rate of the nanoparticles loaded MCC is significantly higher than that of pure MCC due to their low tabletability and high yield pressure, thereby presenting poor plasticity and low compressibility properties. Whereas, 20% loading samples presented improved compressibility compared to 10% loading sample but not as efficient as pure MCC.

Table 3
Parameters derived through curve fitting of tensile strength vs compaction pressure for tabletability, from Ryskewitch–Duckworth equation for compactibility and Heckel coefficient for compressibility, for 10% and 20% API nanoparticle loaded MCC particles; $C_p$ is Tabletability parameter, $\sigma_{t0}$ is tablet tensile strength at zero porosity (MPa), $b$ is empirical constant, $k$ is Heckle coefficient, $P_y$ is yield pressure.

| Loading | Sample | Tabletability | Compactibility | Compressibility |
|--------|--------|---------------|----------------|-----------------|
|        |        | $C_p$ | $R^2$ | $\sigma_{t0}$ (MPa) | $b$ | $R^2$ | $k$ | $P_y$ (kN) | $R^2$ |
| 10%    | MCC    | 1.5  | 0.99 | 11.25 | 6.1 | 0.91 | 0.42 | 2.36 | 0.87 |
|        | CBZ    | 0.99 | 0.99 | 17.88 | 8.3 | 0.97 | 0.23 | 4.37 | 0.97 |
|        | RIS    | 1.0  | 0.97 | 12.96 | 7.9 | 0.90 | 0.21 | 4.74 | 0.62 |
|        | KET    | 1.1  | 0.97 | 11.58 | 8.8 | 0.92 | 0.28 | 3.58 | 0.77 |
| 20%    | CBZ    | 1.02 | 0.99 | 15.84 | 8.4 | 0.97 | 0.34 | 2.97 | 0.93 |
|        | RIS    | 1.5  | 0.98 | 15.97 | 9.6 | 0.96 | 0.30 | 3.35 | 0.96 |
|        | KET    | 1.1  | 0.99 | 15.97 | 9.6 | 0.96 | 0.30 | 3.35 | 0.96 |
loaded API-MCC composite powder comparing with the dissolution of the corresponding physical mixture samples of as-received API. The dissolution of CBZ nanoparticles was enhanced by 3–4 times as compared to the pure CBZ at 5 min, while dissolution of KET nanoparticles was only enhanced by 2–3 times compared to pure KET. The dissolution rate of KET is itself high for a BCS class II drug, therefore nanoparticles of KET influenced the dissolution to a smaller extent compared to CBZ and RIS. Further, the addition of SDS with CBZ formulations could also potentially increase the dissolution rate of CBZ nanoparticles, as was observed for nanoparticle formulations of the

Fig. 7. Compactability profile of the tablets prepared using microcrystalline cellulose (MCC) (blue squares), 10% (left) and 20% (right) API-MCC composites. Red circle for carbamazepine (CBZ-MCC composite), black triangle for risperidone (RIS-MCC composite) and green rhombus for ketoprofen (KET-MCC composite) with n ≥ 3, n is the number of experiments.

Fig. 8. Compressibility profile of the tablets prepared using microcrystalline cellulose (MCC) (blue squares), 10% (left) and 20% (right) API-MCC composites. Red circle for carbamazepine (CBZ-MCC composite), black triangle for risperidone (RIS-MCC composite) and green rhombus for ketoprofen (KET-MCC composite) with n ≥ 3, n is the number of experiments.

Fig. 9. Dissolution profiles of 10% loading and 20% loading of carbamazepine (CBZ) (CBZ + SDS + MCC, filled red triangles), risperidone (RIS) (RIS + MCC, filled green squares) and ketoprofen (KET) (KET + MCC, filled blue circles) obtained using top-spray dynamic bed coater, along with the dissolution profiles of physical mixtures of as-received CBZ (CBZ + SDS + MCC, PhyMix, hollow red triangles), RIS (RIS + MCC, PhyMix, hollow green squares) and KET (KET + MCC, PhyMix, hollow blue circles) with MCC. Curve fitting achieved using Korsmeyer-Peppas model is presented with dotted lines using the respective colors. Dissolution conditions: PHARMATEST FTWS 120D dissolution test system, USP type II (paddle) apparatus. 900 mL, 37 ± 1°C, 100 rpm, [CBMZ]max = 20.0 mg/L, [RIS]max = 15.0 mg/L, [KET]max = 20.0 mg/L, n ≥ 3.

The dissolution rate of KET is itself high for a BCS class II drug, therefore nanoparticles of KET influenced the dissolution to a smaller extent compared to CBZ and RIS. Further, the addition of SDS with CBZ formulations could also potentially increase the dissolution rate of CBZ nanoparticles, as was observed for nanoparticle formulations of the
produce nanoparticles of ketoprofen (KET), carbamazepine (CBZ) and nanoparticles produced was in the range of 90% and 20% theoretical drug loading. The average size of the API dissolution rates of the poorly soluble APIs by following a diffusion release rate constant of 20% loading API samples is approximately 10%meric systems. According to the Korsmeyer-Peppas model, the drug release of RIS which itself is faster dissolving compared to its stable form (Form tors, firstly, nanoparticles of RIS dissolving at a higher rate than the as-

| Loading API Sample | R²     | K ± SD | n ± SD |
|-------------------|--------|--------|--------|
| 10%               |        |        |        |
| CBZ               | 0.983  | ± 36.8 | ± 0.20 |
| MCC_PhyMix        | 2.1    | ± 0.02 |
| CBZ + SDS + MCC   | 0.992  | ± 58.6 | ± 0.13 |
| RIS + MCC_PhyMix  | 1.8    | ± 0.01 |
| RIS + MCC          | 0.982  | ± 1.9  | ± 0.04 |
| KET + MCC_PhyMix  | 20%    | ± 0.68 |
| KET + MCC          | 0.965  | ± 0.23 |
| KET + MCC_PhyMix  | 3.7    | ± 0.03 |
| KET + MCC          | 0.979  | ± 0.20 |
| KET + MCC_PhyMix  | 3.0    | ± 0.02 |
| KET + MCC          | 0.972  | ± 0.17 |
| KET + MCC_PhyMix  | 53.6   | ± 0.02 |
| CBZ + SDS + MCC   | 0.966  | ± 37.5 |
| CBZ + MCC_PhyMix  | 2.87   | ± 0.02 |
| RIS + MCC_PhyMix  | 0.979  | ± 1.2  | ± 0.04 |
| RIS + MCC          | 0.940  | ± 46.6 |
| KET + MCC_PhyMix  | 1.3    | ± 0.03 |
| KET + MCC          | 0.973  | ± 27.4 |
| KET + MCC          | 0.942  | ± 60.1 |
| KET + MCC_PhyMix  | 5.6    | ± 0.03 |

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Table 4 Parameters derived through curve fitting of time vs %dissolution for 10% loading and 20% loading samples of carbamazepine (CBZ), risperidone (RIS) and ketoprofen (KET) using top-spray dynamic bed coater and their physical mixtures from Korsmeyer-Peppas model; K is Korsmeyer release rate constant and n is drug release exponent. SD is the standard deviation.

the uniform coating of API nanoparticles onto the MCC particles. The isolated API-MCC samples presented optimal rheological properties which were confirmed from the tabletability, compactability and compressibility data analysis. Further, a 6–7 fold increase in the dissolution rate of RIS nanoparticles was observed, while 3–4 fold increase for CBZ nanoparticles and 2–3 fold increase for KET nanoparticles. The drug release rate of 20% loading samples is at least 10% higher compared to 10% loading samples. Hence, top spray dynamic bed coating using supercritical CO₂ as the atomizing gas is a novel method which provides a single-step approach to produce and isolate solid nanoparticles with optimal dissolution and rheological properties.

CRediT authorship contribution statement

Vivek Verma: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. Kevin M. Ryan: Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition. Luis Padrela: Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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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A major enhancement in the dissolution was observed for RIS. The dissolution of RIS nanoparticles was enhanced by 6–7 times compared to the pure RIS. The enhancement in RIS dissolution is based on two factors, firstly, nanoparticles of RIS dissolving at a higher rate than the as-received RIS, and secondly, due to the metastable polymorph (Form B) of RIS which itself is faster dissolving compared to its stable form (Form A).

Further, the drug release curves were fitted using the Korsmeyer-Peppas model, which is useful for the study of drug release from polymeric systems. According to the Korsmeyer-Peppas model, the drug release rate constant of 20% loading API samples is approximately 10% higher compared to 10% loading samples, as presented in Table 4. Further, the drug release constant (n) value for all the samples obtained using the top-spray dynamic bed coater is less than the threshold for the Korsmeyer-Peppas (n = 0.43) (Peppas, 1985). Hence, the nanoparticles generated using top spray dynamic bed coating process help to enhance the dissolution rates of the poorly soluble APIs by following a diffusion controlled release mechanism.

4. Conclusions

The ‘top spray dynamic bed coater’ was successfully operated to produce nanoparticles of ketoprofen (KET), carbamazepine (CBZ) and risperidone (RIS), and coat them onto micron-sized MCC particles with 10% and 20% theoretical drug loading. The average size of the API nanoparticles produced was in the range of 90–490 nm with high processing yields of 49–90%. PXRD analysis confirmed the production of crystalline nanoparticles which were coated onto MCC particles with stable polymorphic forms for CBZ and KET, while metastable form for RIS. The Scanning Electron Microscopy (SEM) micrographs confirmed
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