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Enhancement of material attributes of poorly compressible metformin hydrochloride through coprocessing with hydroxypropyl cellulose (HPC-L) using coprecipitation (CPT)

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Abstract

Coprocessing involves integration of multiple substances to improve the physical, chemical, mechanical, and biopharmaceutical properties of a material. Coprocessing is a promising technique in the pharmaceutical industry which support both drug substance and drug product processes. When active pharmaceutical ingredients (APIs) are coprocessed with excipients, it can enable direct compression and continuous manufacturing. Hydroxypropyl cellulose (HPC-L), a commonly used excipient in pharmaceutical formulations, can enhance drug stability, solubility, and bioavailability. In this study, we have employed coprecipitation (CPT) to coprocess metformin hydrochloride (MET) with HPC-L, resulting in the formation of agglomerates with improved physical attributes without any risk of polymorphic changes. Acetone/acetonitrile and heptane were used as solvent and antisolvent, respectively. Screening study revealed that the use of a rotor stator helps to control the size of metformin hydrochloride and HPC-L agglomerates (M-CPT) without negatively impacting bulk density and powder flow properties. The CPT agglomerates showed residual solvent levels within the specified ICH limits. Powder rheology results demonstrated a sixfold increase in FFC of M-CPT compared to neat MET. The compressibility, tabletability, compactability, and "In-Die" Heckel analysis data further suggested that the M-CPT agglomerates are directly compressible with no observable changes in the dissolution profile of MET. Overall, this study demonstrates application of CPT approach to tune the physical and mechanical properties, and HPC-L can be used as an excipient of choice for CPT technique to improve the compressibility and flowability of APIs.

Keywords Metformin hydrochloride, Coprocessing, Coprecipitation, Direct compression, HPC-L

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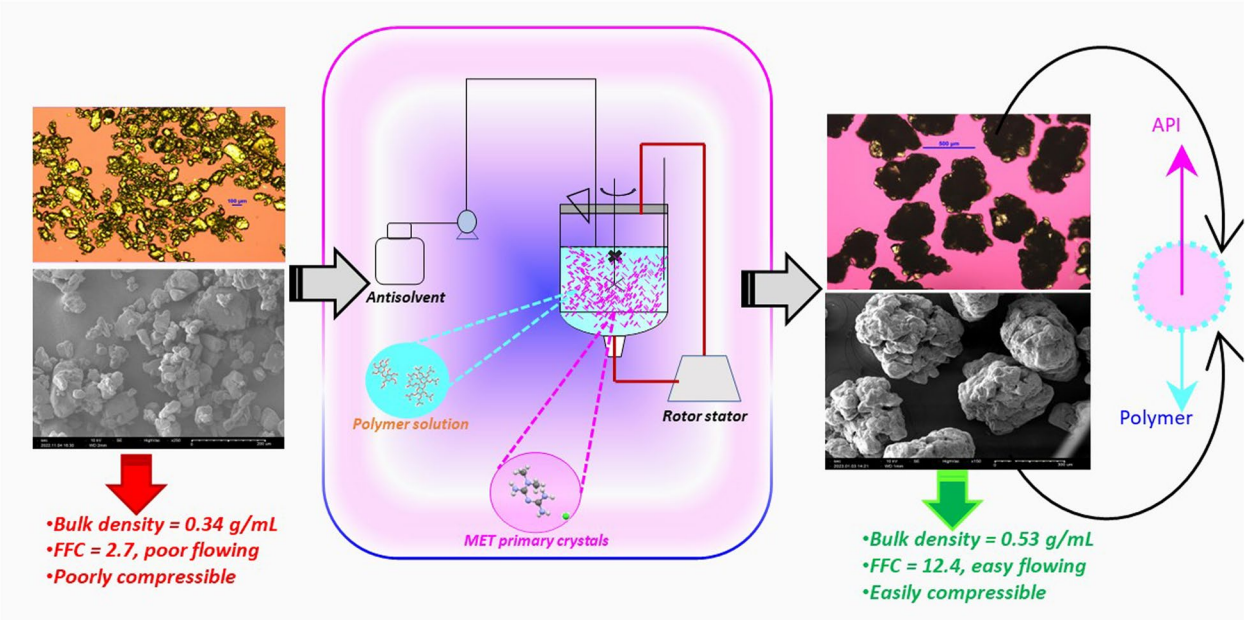
Graphical Abstract



Introduction

The process of combining two or more substances to create a material with enhanced physical, chemical, mechanical, and biopharmaceutical properties is known as coprocessing (Rojas et al. 2012; Schenck et al. 2020). Essentially, coprocessing involves particle engineering that modifies the critical material attributes (CMA) of the primary substance. These changes in the CMA result in creation of coprocessed material with improved functionality. In the pharmaceutical industry, coprocessing is very common among excipient manufacturers to enhance the functionality of excipients, which are ultimately used in the drug product manufacturing (Saha and Shahiwala 2009; Gupta et al. 2006).

In recent years, coprocessing of APIs (active pharmaceutical ingredients) with excipients or second APIs has gained significant attention due to its ability to achieve the desired properties. The improved functionalities in coprocessed APIs enable first hand application of direct compression by bypassing granulation in first place and enable continuous manufacturing (Paul 2023; Erdemir 2022). In some cases, coprocessed APIs also exhibit improved solubility, dissolution rate, and stability (Schenck et al. 2021). Coprocessing methodologies used by the pharmaceutical industry are discussed in detail in recent publications and can be categorized into three main types: before crystallization, during crystallization, and after crystallization (Schenck et al. 2020). This study focuses on coprecipitation, which is done after the API crystallization. Coprecipitation involves polymer precipitation or coating on the drug crystal surface, resulting in the formation of spherical agglomerates with the desired size, shape, and morphology, improved flowability, and effective avoidance of the granulation step (Erdemir et al. 2019; Prosapio et al. 2016). HPC-L is a type of hydroxypropyl cellulose polymer that is non-ionic, hydrophilic, and has a low viscosity grade (Sarode et al. 2013). It is commonly used as an excipient in pharmaceutical formulations to improve drug stability, solubility, and bioavailability. In this study, the coprocessing of HPC-L with metformin hydrochloride (MET), a model poorly compressible API, was demonstrated using the coprecipitation technique, which allowed the fabrication of spherical agglomerates with improved bulk density and flowability, enabling the direct compression. MET exhibits poor compressibility due to its low bulk density, poor flow properties, and high interparticle cohesion, resulting in low tablet hardness, irregular shape, and difficulties in handling, packaging, and administration (Bhatt et al. 2020). Current approach for overcoming these issues is by using wet/dry granulation techniques (Tank et al. 2018). However, this involves multiple unit operations during manufacturing. Therefore, coprocessing can be

suitable technique to improve flowability and enable direct compression.

Prior studies have used the coprecipitation approach with polyvinylpyrrolidone-based polymers, as well as some studies reported the coprocessing of MET using crystallization in polymer matrix, QESD crystallization, spherical crystallization, and spray drying (Hansen and Kleinebudde 2022; Erdemir et al. 2018; Barot et al. 2012; Al-Zoubi et al. 2017). To the authors' knowledge, there has been no publication that demonstrates the use of HPC-L as a coprecipitating agent or the reported solvent system to prepare directly compressible material.

The aim of this study was to fabricate and investigate in detail the usability of HPC-L as a coprecipitating agent. This will help researchers to choose from a broader range of excipients for coprocessing APIs with poor flow. In order to prepare spherical agglomerates, coprecipitation of HPC-L on the drug crystal was ensured by careful selection of solvent, antisolvent, temp, and wet media milling. Coprocessing of MET with HPC-L is aimed to provide spherical agglomerates with improved morphology, bulk density-flowability, no changes in the crystalline form of MET, and dissolution profile. In the current work, the possibility of using HPC-L was explored to prepare coprocessed particles capable of improving material attributes of API.

Material and methods

Materials

Metformin hydrochloride (MET) was purchased from Letco Medical (AL, USA). Hydroxypropyl cellulose-L (HPC-L) was from Nisso America (NJ, USA). The process solvents used were acetone, acetonitrile, and heptane and were analytical grade purchased from Sigma-Aldrich (MO, USA).

Coprocessing of MET with HPC-L using coprecipitation technique

General overview

Screening and scale up experiments were carried out using EasyMax 102 and 402 with dosing unit, respectively. All vessels were jacketed to control temperature with overhead shaft and pitch-blade element metal stirrer. For in-line monitoring during the screening batches, BlazePAT 900 probe was used. Probe is equipped with image-derived chord length distribution to track particle size and count. The solubility of MET in acetone and acetonitrile was less than 2 mg/mL. Solvent amount used is reported in vol, has units of mL/g (mL of solvent/kg of MET). Typical amount of HPC-L used was 20 wt% with respect to the total solids input. In these processes, HPC-L was dissolved in 7.9 vol of acetone to make clear to hazy solution followed by 1.6 vol of acetonitrile was added to the solution and aged for 0.5–1.0 h at 20 °C. To the polymeric solution, MET was added to the system and aged for 0.5–1.0 h at 20 °C. The polymer HPC-L was precipitated as 20.5 vol of heptane dosed into the system. Precipitated HPC-L coats the suspended MET crystals leading to spherical agglomerate formation. At the end of the CPT process, total heptane added amount constitutes to 69 vol%. Before filtration of slurry, system was decanted several times to reduce the total acetone/acetonitrile contents. After several decantation, slurry was filtered via positive pressure filtration followed by vacuum drying at 40 °C.

Screening study

CPT process was designed and optimized in two stages: (1) screening study, and (2) reproducibility study. Screening study was conducted using 0.1L Easymax reactor. Purpose of the screening study was to determine process parameters and polymer loading to form spherical agglomerates with improved flowability and bulk density. General process involved dissolving 0.85 g of HPC-L in $85{:}15_{(v/v)}$ of acetone/acetonitrile (33.5 mL; 9.8 vol). Afterwards, 3.4 g of MET was suspended and aged for 0.5 h at 20 °C at 800 rpm followed by addition of heptane (70 mL; 20.5 vol) at the rate of 0.38 mL/min. After complete heptane addition, system was left overnight for aging, and next day, several decantation were carried out using heptane, followed by filtration and vacuum drying. Based on the outcomes of the screening studies, process parameters were determined and used for next set of experiments to understand the impact of wet-milling on formed spherical agglomerates. The CPT process parameters were kept same as discussed above. The additional step during these experiments was intermittent wet-milling. Wet-milling was done using IKA homogenizer at 12,000 rpm after 10, 20, 25, 35, and 50% of heptane addition. During the wet-milling, heptane addition was paused and milling was done for 2 min/stage. After complete heptane addition, batch was aged overnight followed by decantation using heptane. Before decantation, vessel agitation was stopped leading to agglomerates settling and leaving clear supernatant liquid. CPT solids (M-CPT) were settled very fast once the agitation was stopped. The supernatant clear liquid was removed without disturbing the agglomerate bed settled at the bottom of the vessel. Approximately 80% of solvent was removed during each decantation and replaced by the fresh heptane. Decantation was carried out to reach to < 2 vol% of acetone. Between each decantation, batch was aged for 0.5 h at 800 rpm. After decantation, batch was filtered

and washed with heptane followed by vacuum drying at 40 °C.

Reproducibility study

After completion of screening studies at 4.0 g scale, reproducibility study was conducted at 30.0 g scale using Easymax 402. Based on the screening studies, process parameters were determined and used in the reproducibility study. Optimized polymer loading was found to be 20 wt% of the total solid input; therefore, the ratio between MET/HPC-L was kept constant to $80{:}20_{(wt/wt)}$. Scale up process involved dissolving 7.5 g of HPC-L in $85{:}15_{(v/v)}$ of acetone/acetonitrile (149.0 mL; 9.8 vol). Afterwards, 30.0 g of MET was suspended and aged for 0.5 h at 20 °C at 700 rpm followed by addition of heptane (250 mL; 20.5 vol) at the rate of 1.38 mL/min. Slurry was wet-milled using handheld homogenizer at 12,000 rpm after 10, 20, 25, 35, and 50% of heptane addition. During the wet-milling, heptane addition was paused. After complete heptane addition, system was left overnight for aging and next day several decantation were carried out using heptane as mentioned in screening study section. After decantation, agglomerates were filtered, washed, and vacuum-dried at 40 °C.

Analytical test methods

Differential scanning calorimetry

A differential scanning calorimeter (DSC-2500, TA Instruments, White Castle, DE) was used to measure heat flow associated with physicochemical transitions of MET and M-CPT as a function of temperature. Instrument was calibrated for temperature and heat capacity using indium and sapphire, respectively. Sample weights (5–10 mg) were placed in a hermetic sealed aluminum pan with a pinhole. Sample was heated at a ramp rate of 10 °C/min from 20 to 250 °C with a 50 mL/min dry nitrogen purge.

Thermal gravimetry analysis

A thermogravimetric analyzer (TGA-5500, TA Instruments White Castle, DE) was used to determine % wt loss as a function of temperature. Samples weighing approximately 5–10 mg were placed in a hermetic aluminum pan with a pinhole. Sample was heated at a ramp rate of 10 °C/min from room temperature to 250 °C with a 50 mL/min dry nitrogen purge.

Powder X-ray diffraction

Powder X-ray diffractometry (PXRD) patterns were obtained using an Empyrean X-ray diffractometer (Malvern Panalytical, Westborough, MA). Cu K-α radiation was generated at 44 kV and 40 mA. The samples were scanned from 2 to 40° 2θ at a scan speed of 6.66°/min in the Bragg Brentano geometry.

Morphology and surface analysis

A field emission scanning electron microscope (SNE-4500 M Plus, Nanoimage, Lafayette, CA) operating at 10 kV accelerating voltage was used to characterize the morphology of MET and M-CPT. Samples were prepared on the conventional scanning electron microscopy holder with the carbon tape, and sputter-coated with gold. Polarized light microscopy (ECLIPSE Ci-POL, Nikon, Melville, NY) images were acquired to capture the change in the particle's morphology and surface during the CPT process as well as of dry product.

Raman imaging analysis

The powder chemical mapping to determine agglomerate composition was conducted by Raman imaging with a Raman microscope (XploRA™ Plus, Horiba, NJ) equipped with 532-, 638-, and 785-nm laser. Raman spectra of metformin HCl, HPC-L, and the coprocessed material were collected in the 50–3500 cm^{-1} range. Analytical range for metformin HCl and HPC-L used was in the range of 600–670 nm and 830–890 nm, respectively.

In-line microscopic monitoring

CPT screening batch was visualized by high-resolution inline imaging using a Blaze900 probe from BlazeMetrics. The probe has a field of view of 900 μm, uses a 532-nm laser, and the image plane was set to 80 μm.

Particle density analysis

The bulk density of the M-CPT was measured by gently transferring the powder into a graduated cylinder and calculating the ratio of the mass of the powder to its volume. Tapped density was determined using USP method-I where graduated cylinder filled with material was tapped 1250 times and calculating the ratio of the mass of the powder to its volume. Bulk and tapped density were used to determine the Carr's index and Hausner ratio values. The particle density was determined using AccuPyc II 1345 (Micromeritics, Norcross, GA) in triplicate. Samples were purged with ten repetitive cycles before recording each data point.

Particle size distribution analysis

The particle size distribution (PSD) of the starting material and M-CPT was analyzed using wet dispersion dynamic image analysis (Mastersizer 3000, Malvern Panalytical, UK). Carrier fluid and sample dispersion media used was 0.1 wt% lecithin in heptane. Approximately

200 mg solid sample was dispersed in 10 mL dispersant. Before the measurement, sample was vortexed for 30 s followed by sample addition to sample chamber to achieve 5–20% obscuration. Measurement was done in triplicates with 10 s durations for each measurement.

Powder rheology

The FT4 powder rheometer was used to determine flow function coefficient (FFC) as a measure of flow improvement between unprocessed neat MET and M-CPT. The flow function coefficient (FFC) is defined as the ratio of the major consolidation stress to the uniaxial compressive strength. Powders were added in 25 mL shear cell module and conditioned before applying pre-consolidation normal stress of 15 kPa with a 25 mm flat-surface vented piston. Shear stress needed to cause powder particles start to move relative to one another, as function of the applied normal stress were obtained at a normal stress of 5, 6, 7, 8, and 9 kPa. Five data points obtained can be plotted in a two-dimensional coordinate and a yield locus was obtained using FT4 Powder Rheometer software version 4.0 (Freeman Technology Ltd., Tewkesbury, UK).

Granule integrity test

First, the coprocessed material was manually sieved through 14, 30, 60, 150, 200, and 325 mesh screens. The weight percentage of particles in each size range was determined. Depending on the bulk density, the fill level in the container is normally between 40 and 60%. The material was subjected to low-frequency, high-intensity acoustic energy (73G), which created a uniform shear field throughout the entire mixing vessel for 3 min (LABRAM; Resodyne Acoustic Mixers, Butte, MT). Next, the sieve analysis was repeated to determine the weight percentage of particles in each size range after the application. The GIT index was calculated by taking the difference between the weight percentages of particles greater than 250 μm before and after the exposure to high-intensity resonant acoustic energy.

$$\mathrm{GIT} = \frac{(Po - Pf)}{Po} \tag{1}$$

The GIT index was calculated using following equation, where Po and Pf are the weight percentages of particles larger than 250 μm before and after the application of high-intensity acoustic energy (73G), respectively.

High-performance liquid chromatography

Determination of MET potency in the M-CPT material and dissolution sample analysis was carried out using high-performance liquid chromatography (HPLC) analysis. The HPLC was performed by isocratic reverse-phase LC using UV detection (Agilent 1260, Santa Clara, CA). HPLC column used in this study was Xbridge C18 (5 μm, 4.6×250 mm). Mobile phase used was 90: $10_{(v/v)}$ of sodium 1-pentanesulfornate buffer (pH = 2.5) and acetonitrile. Analysis parameters were flow rate (1 mL/min), column temperature (30 °C), injection volume (5 μL), and analytical wavelength (218 nm). M-CPT samples were prepared at concentrations of 0.2 mg/mL MET in the diluent and analyzed against a reference material with the same concentration.

Gas chromatography and oven Karl Fischer (KF) analysis

M-CPT samples were analyzed for residual acetone and heptane using headspace GC with a flame ionization detector (Agilent HP 6890, Santa Clara, CA). Solvents were quantified by weight percent (% w/w) on a total M-CPT sample weight basis. The water content of M-CPT was monitored by oven Karl Fischer (860 KF Thermoprep, Metrohm, Palm River-Clair Mel, FL).

Powder mechanics

Tableting

The CPT materials were compressed into tablets using a compaction simulator (Styl'One Nano, Medelpharm, France) equipped with 11.28 mm flat-faced punches. Material used for the compression studies is from the reproducibility batch. Approximately 500 mg powder sample was manually filled into the die and the powder was compacted between 50 and 400 MPa compaction pressure without using dwell time. Ejected tablets were stored in a desiccator at room temperature for 24 h to allow for complete elastic recovery. Compact mass and dimensions measured after 24 h after ejection were used to compute compact density, solid fraction, and porosity. Neat metformin HCl was not compressible at any given compression pressure which aligns with the findings in the previous works. The tablet breaking force was measured using tablet hardness tester (Natoli hardness tester, PA). The tablet tensile strength was calculated using the following equation:

$$\sigma = \frac{2F}{\Pi DT} \tag{2}$$

where σ is the tablet tensile strength (MPa), F is the tablet breaking force (N), D is the tablet diameter (mm), and T (mm) is the tablet thickness.

Simulation to rotary tablet press

A Korsch XL400 rotary tablet press was simulated on the Styl'One to analyze the influence of a precompression step on the tablet strength at a speed of 47 rpm (= 98,700 tablets/h). Precompressions were set from 30 MPa and

combined with main compressions of 200 MPa. Furthermore, the influence of the tableting speed was analyzed by compressing tablets at simulated speeds of 98,700 tablets/h at 30/200 MPa pre- and main compression. This was equivalent to 47 rpm of the turret speed.

In-die Heckel analysis

Coprocessed M-CPT compression performance was evaluated using material sparing, fast, simple, and accurate "in-die" Heckel method. Before the compression analysis, material was sieved to mitigate the effect of disparate particle size distributions on the material compressibility. The die was filled with a predetermined constant particle volume of each material, as the movement of the punch is influenced by the volume of powder in the die cavity. Compression of the powders was carried out using a "saw-tooth" profile, maintaining a constant compression pressure of 100 MPa. The resulting compacts were then weighed using an analytical balance. The Heckel parameters were determined based on the force–displacement data. The linear portions of the compression and decompression phases of the graph were identified using a straight-line equation, allowing the calculation of the corresponding yield pressure values for deformation.

Dissolution

Dissolution of 480 mg strength metformin hydrochloride tablets (equivalent to 600 mg tablet) from a reproducibility batch ($n=6$) was conducted in 1000 mL of 50 mM phosphate buffer (pH 6.8) at 37 °C using the USP apparatus I at 100 rpm. The tablets were compressed using precompressions of 30 MPa and combined with main compressions of 200 MPa. Chosen tablets exhibited a tensile strength ranging from 2.1 to 2.3 MPa and a solid fraction exceeding 0.9. At the specified time interval (5, 15, 30, 60, and 180 min from initiation of the test), an approximately 5.0 mL aliquot was removed from each dissolution vessel and filtered using a 0.45 µm PVDF filter. The amount of metformin dissolved was determined using a UV–vis spectrometer and computed using the UV–vis Chemstation software.

Results and discussion

Coprocessing of metformin hydrochloride with HPC-L using CPT

Screening studies were carried out to evaluate the impact of process parameters and polymer loading on the final solid-state characteristics. As the focus of this paper is not on the detailed screening study data, therefore, only essential process parameters are discussed. The CPT test was conducted at a 3.42 g API level using an acetone/acetonitrile solvent system. The total heptane was added over the period of 3 h with agitation at 20 °C, followed by overnight aging. PLM/SEM analysis indicated that the formed agglomerates were densely packed with a smooth surface, and the average size of the agglomerates was greater than 450 µm. When wet milling was incorporated into the CPT, the formed agglomerates were smaller compared to the unmilled batch, as observed by PLM and SEM. The Blaze 900 instrument was utilized to monitor alterations in particle size distribution throughout the course of the process. The pattern is presented in Fig. 1. In a typical procedure, metformin HCl inherent particles were observed prior to heptane addition. As reported earlier, HPC-L was completely dissolved in $85{:}15_{(v/v)}$ of acetone:acetonitrile. However, HPC-L does not dissolve in heptane, which functions as an antisolvent, inducing polymer precipitation. As the quantity of heptane rises, so does the polymer precipitation. It is also noteworthy that MET has a solubility of less than 2.0 mg/mL in the chosen solvent:antisolvent mix. Once the heptane addition was started, there was a gradual decrease in the count of particles with a chord length of 1–120 µm. The count for small-medium particles decreased and, simultaneously, the count for large particles increased (140–660 µm chord length). The data regarding particle count trend suggests that there are "3-critical points" in the process. The first critical point occurs after the addition of 9.7% heptane where the count of small particles decreased more rapidly. The second critical point occurred after the addition of 16% heptane where the count of medium and large particles increased significantly, and the average size also increased. The third critical point occurred after the addition of 25.5% heptane where the count of medium particles decreased more rapidly and the count of large particles showed a sharp increase. The overall results suggest that, as the amount of heptane was increased, the particles adhered together due to the precipitation of HPC-L, resulting in the formation of agglomerated material. Interestingly, there was a point in the process where the particle agglomerates reached their maximum size. Real-time images were captured as the process progressed, and the data is presented in Fig. 2. Based on the images, it can be concluded that the addition of heptane caused the particles to adhere together to form larger agglomerated particles. It is important to note that real-time particle count and image data were collected without using a rotor stator. The author recognizes that the use of wet milling in conjunction with the process may result in changes in the critical point with respect to the amount of heptane added due to additional stress caused by particle attrition in the wet mill. However, we anticipate that this kinetic change may not be significantly different from the current trend. The reproducibility of the screened

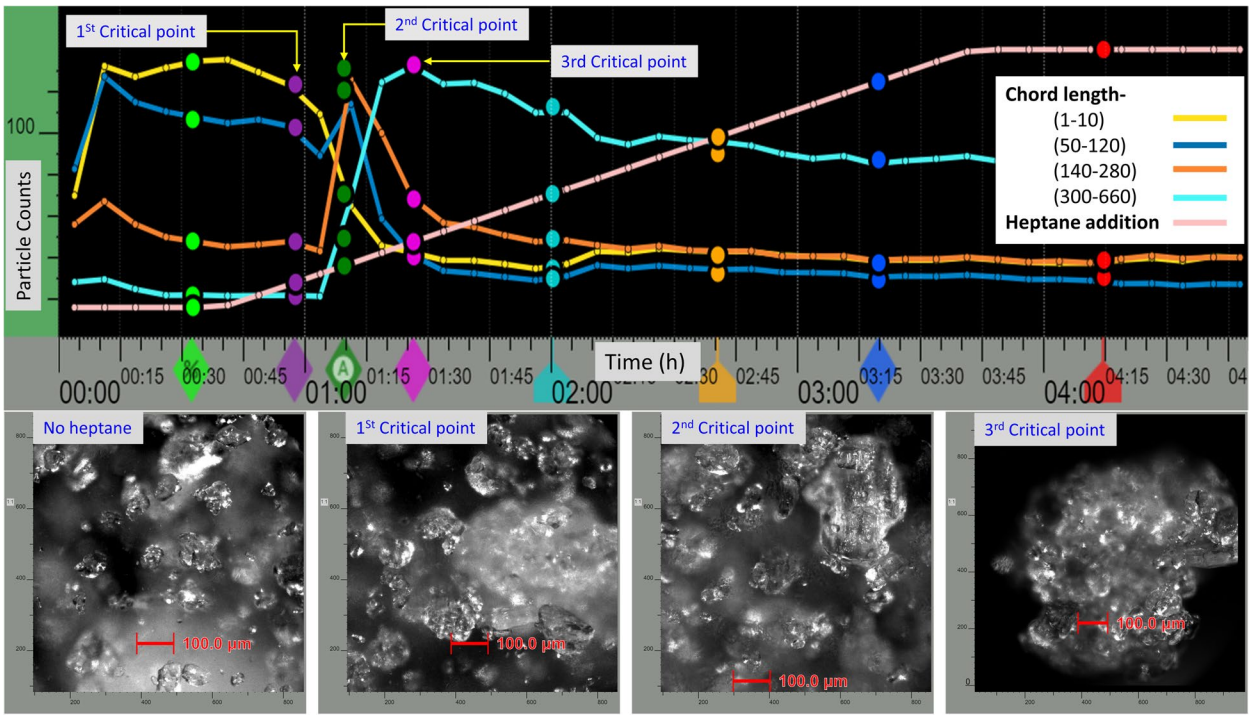


Fig. 1 Blaze metrics in situ data of CPT process without the wet milling

CPT method was successfully tested at the 30.0 g API level. The total amount of heptane was added with agitation over a period of 3 h at 20 °C, and intermittent homogenization was applied. The batch was left to age overnight, and PLM and SEM showed dense agglomerates with a smoother surface. Wet-milling is prevalently employed in crystallization and coprocessing, because of its high shearing attributes. Wet milling offers several advantages including enhanced mixing, optimized heat transfer, reduced nucleation time, and superior control over particle size. However, a primary challenge in utilizing wet-milling is inappropriate process parameters and rotor stator configurations leading to generation of undesired shear stress, potentially resulting in over-milling or under-milling of the crystals. In summary, wet-milling offers great advantage in coprecipitation for generating denser agglomerates with controlled particle sizes.

Characterization of coprocessed material

Solid-state characterization, residual solvent and water content determination

Attaining the intended solid form is crucial to successfully develop and market a drug product with the desired therapeutic efficacy. In CPT process, material was slurried in organic solvents and put under shear stress during wet-milling; therefore, it was imperative to understand the impact solid-state property of the active pharmaceutical ingredient, i.e., MET. Various solid-state characterization techniques, such as PXRD, DSC, and TGA, were employed to evaluate the solid-state properties of the drug substance. Figure 3 displays the PXRD diffractogram of the starting material and CPT material. The PXRD diffractogram of M-CPT from both the milled and unmilled batches matched with the MET, implying no change in crystalline form. Additionally, based on the pattern, it can be inferred that the agglomerates possess crystallinity similar to the starting material. The diffractogram from the reproducibility batch demonstrated similar outcomes, indicating the robustness of the developed CPT method.

DSC and TGA analyses were conducted on both the starting material (MET) and M-CPT products. The neat MET displayed a distinctive melting endotherm at 234.3 °C, and the TGA curve revealed no weight loss between room temperature and 100 °C, indicating the anhydrous nature of the material (Fig. 4). The overlaid DSC and TGA of CPT showed a distinct melting point at 232.5 °C with a smooth baseline, suggesting that no hydration, solvation, or polymorphic transition events occurred during the treatment process. Similarly, no weight loss was observed during TGA heating between room temperature and 100 °C, indicating that the CPT end products remained in an anhydrous form (Fig. 5). However, the melting point peak and fusion enthalpy of

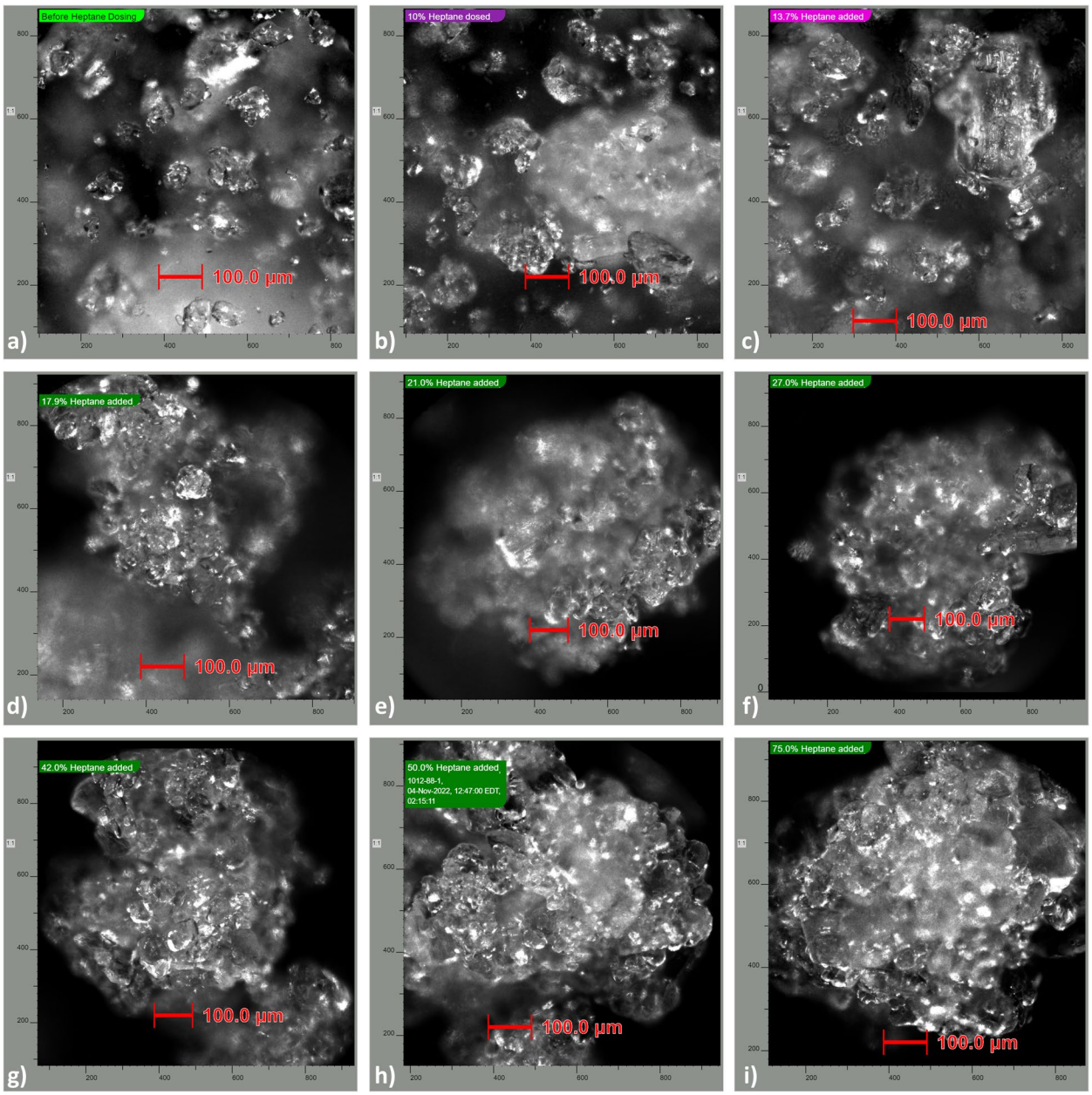


Fig. 2 Blaze metrics in situ image data (CPT without wet milling): **a** before heptane addition, **b** 10% heptane, **c** 13.7% heptane, **d** 17.9% heptane, **e** 21% heptane, **f** 27% heptane, **g** 42% heptane, **h** 50% heptane, and **i** 75% heptane added

M-CPT decreased by 1.8 °C and 50.02 J/g, respectively, in comparison to MET. This reduction in melting point temperature and fusion enthalpy may be due to the physical interaction between MET and HPC-L, resulting in changes in physical properties. In conclusion, the solid-state characterization data suggest that there was no significant change in the solid-state properties of M-CPT, including polymorphic transitions.

In coprecipitation, it is important to determine residual solvent and water content for quality and safety reasons. Residual solvents and water can affect the quality, purity, and stability of the final product. Therefore, determining their content is crucial to ensure that the product meets the required specifications and is safe for human use. The residual solvent content was determined using gas chromatography which has quantitation limit of 5 ppm. Results showed that the sample contained no detectable

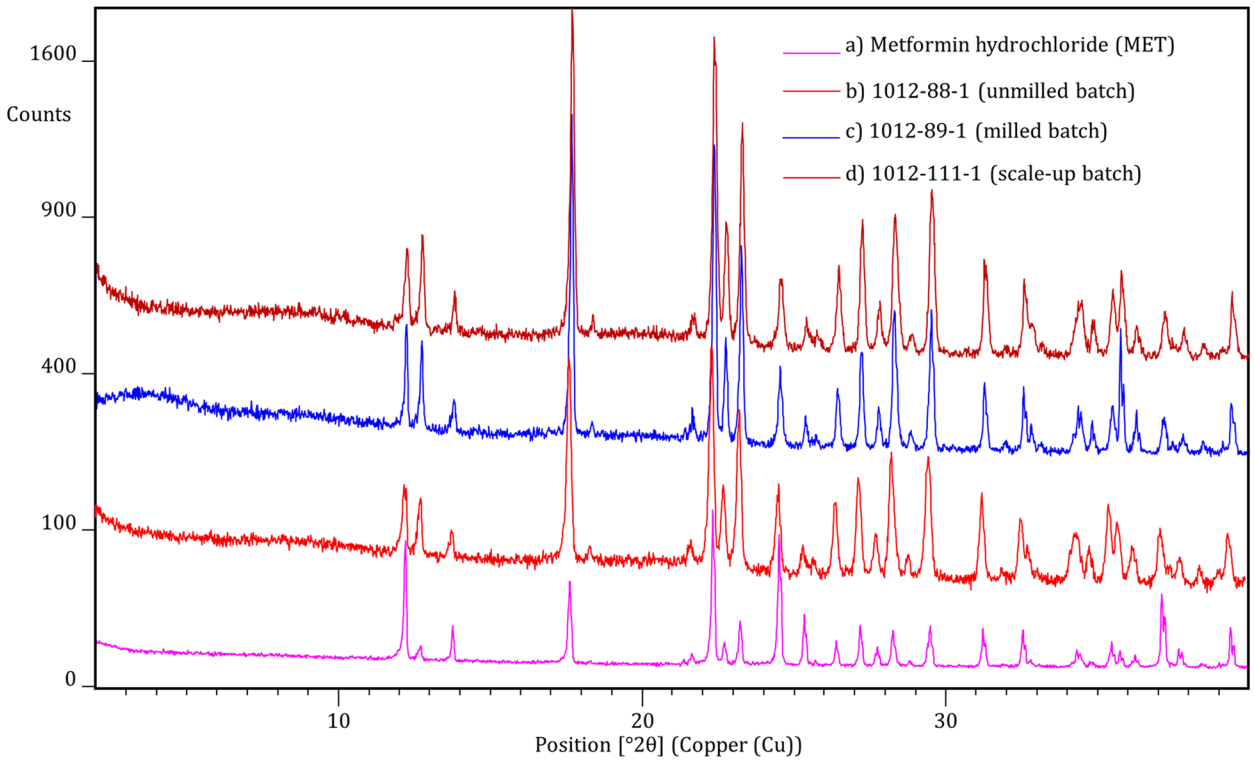


Fig. 3 PXRD diffractograms of (**a**) starting material (MET), (**b**) M-CPT (unmilled batch), (**c**) M-CPT (wet-milled batch), and (**d**) M-CPT from reproducibility up batch

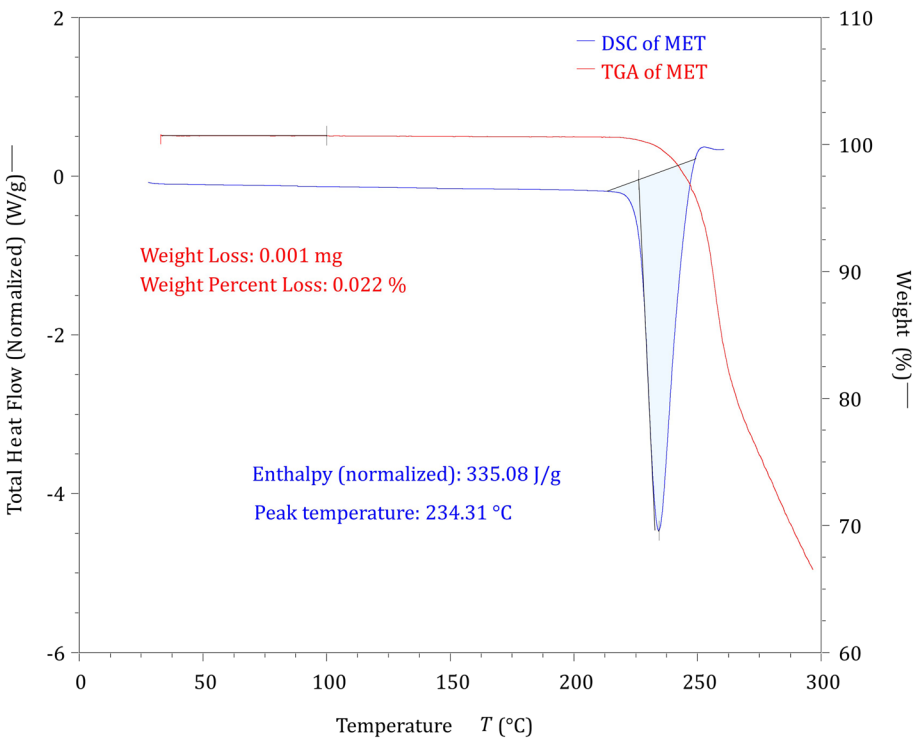


Fig. 4 Overlaid DSC and TGA of starting material (MET)

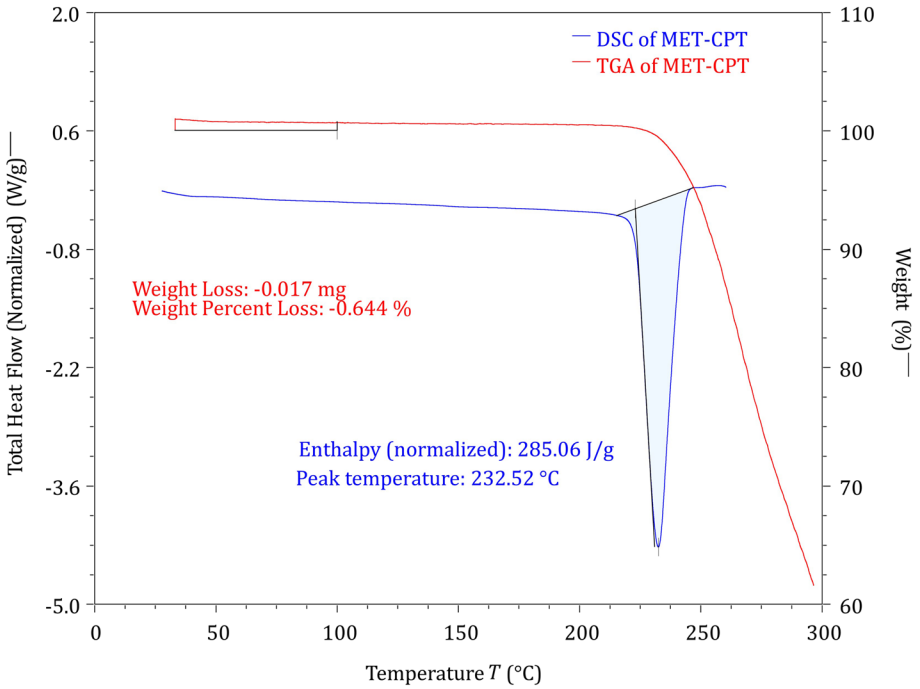


Fig. 5 Overlaid DSC and TGA of coprecipitated material of M-CPT

amount of acetone, acetonitrile, and 0.12 wt% of heptane (ICH class III solvent). The Karl Fischer method was employed to determine the water content, and the data showed that the sample contained 0.6 wt% of water. These results indicate that the sample meets the required specifications for residual solvent and water content levels.

Morphology, size and drug distribution uniformity

To ensure consistent flowability of drug particles, it is critical to ensure uniformity of morphology, size distribution, and drug distribution. Some of the methods reported for coprocessing APIs with excipient provide limited control over agglomerates morphology and surface properties, leading to the formation of irregular agglomerates with non-uniform drug loading and wide size distributions. However, the CPT approach reported here produced agglomerates with specific shape, unlike the neat MET powder, which was fine and irregularly shaped. As showed in Figs. 6 and 7, both the unmilled and milled batch of CPT-MET crystalline microparticles generated showed uniform approximately spherical shape under PLM and SEM imaging. Similar observations were observed with the reproducibility batch material.

Particle size distribution was analyzed using wet dispersion dynamic light scattering and plotted as a distribution curve (Table 1). The neat MET powder had the smallest particle size and highest span, while all CPT-generated particles exhibited a unimodal size distribution with larger average particle sizes and significantly reduced span values. Co-precipitated material showed a significant increase in D_{50} compared to the starting material (893 vs. 84 µm). When the CPT material was subjected to rotor stator, a decrease in D_{50} was observed compared to the unmilled CPT (461 vs. 893 µm) (Fig. 8). The reduction in agglomerate size in the milled batch was due to the shear stress generated by the rotor stator. However, based on the PLM and SEM data, it was evident that the agglomerates' morphology and surface characteristics did not change compared to the unmilled batch. The only change observed was the significant reduction in agglomerate size with the use of the rotor stator. Based on the data, it can be concluded that desired sizes of agglomerates can be prepared using CPT with appropriate wet milling parameters. The size and shape uniformity of coprocessed microparticles can be attributed to the precipitation of the polymer onto the drug particles, leading to the agglomeration of the drug crystals.

Confocal Raman mapping was utilized to verify the uniformity of polymer distribution within particles, specifically M-CPT agglomerates. The process involved recording Raman spectra for neat microparticles using a 532-nm excitation laser and identifying Raman shifts specific to MET and HPC-L between 700–770 and 830–890 cm^{-1}, respectively. These peaks were found

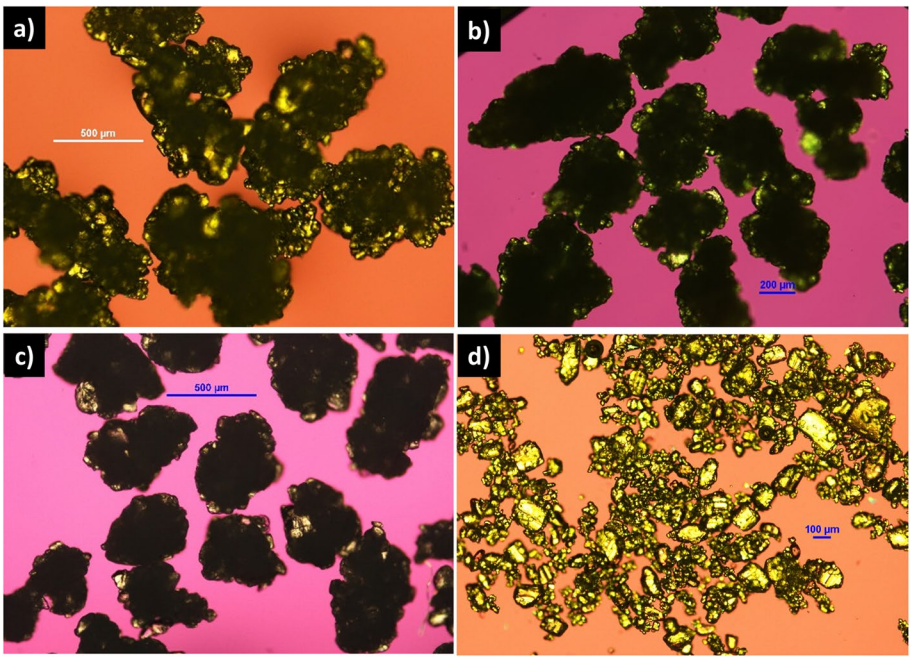


Fig. 6 PLM images of (**a**) M-CPT (unmilled batch), (**b**) M-CPT (wet-milled batch), (**c**) M-CPT from reproducibility up batch, and (**d**) starting material (MET)

at both the surface and the confocal depth of approximately 150 µm for M-CPT agglomerates, although the peak for HPC-L was weaker due to its smaller proportion in M-CPT agglomerates. Point-by-point mapping was then conducted, generating x–y maps using the drug to polymer intensity ratio, which highlighted uniform drug distribution at the surface of approximately 150 µm for M-CPT agglomerates. The Raman imaging in Fig. 9 demonstrated the intimate mixing of HPC-L and MET, and no chemical interaction was observed between metformin and HPC-L after coprocessing. The coprocessed material showed the same spatial distribution for metformin and HPC-L, indicating that they occupy the same location and are physically embedded in each other.

Performance characteristics

Powder density, flowability and granule integrity testing

In pharmaceutical manufacturing, ensuring powder flowability is crucial because poorly flowing powders can lead to inconsistent powder dispensation. This, in turn, can affect the uniformity of tablet. Therefore, powder flowability is a major concern in pharmaceutical manufacturing. Standard methods were employed to determine the bulk density, tapped density, and Hausner ratio of the powder. The results showed that the bulk density of MET and M-CPT were 0.35 g/cm^3 and 0.53 g/cm^3, respectively. Furthermore, the Hausner ratio for MET and M-CPT was found to be 1.36 and 1.12 respectively, which was calculated as the ratio of the tapped density to the bulk density. These findings suggest that coprecipitation resulted in a notable increase in the bulk density, which indicates good flowability and compressibility in comparison to MET. These results were further supported by flow function coefficient test using an FT4 powder rheometer.

To investigate the flow behavior of MET and M-CPT, powder flow rheometry was used to obtain incipient failure or yield points as a function of the applied normal stress. Figure 10 illustrates the plot for the incipient shear stress of powder flow as a function of the applied normal stress for each of the three powder samples, while the inset table summarizes the flowability metrics. Neat MET with a cohesion value of 2.6 kPa and a flow factor of 2.7 was the most cohesive and least flowable. Comparatively, coprecipitated agglomerates of M-CPT had a significant reduction in the cohesion value (0.65 kPa), and a significant increase in the flow factor to 12.4, putting them in the "free-flowing" category (Leturia et al. 2014).

The GIT was used to assess the strength of coprocessed agglomerates, with results presented in Table 2. An index value of <0.1 was obtained, indicating that the agglomerates are robust and less likely to undergo attrition or segregation during downstream handling. A GIT index value of 0 denotes full granule integrity, while values below 0.3

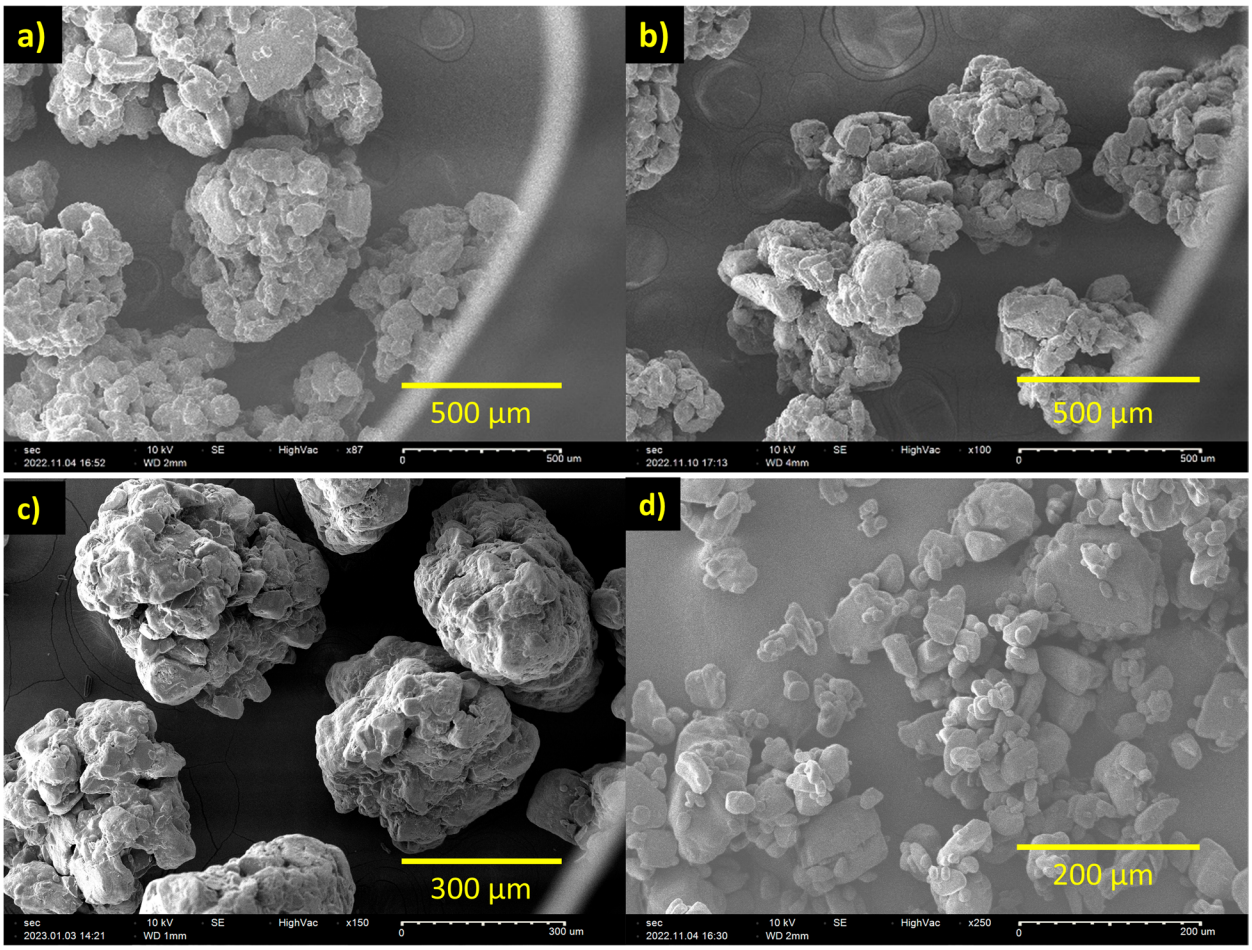


Fig. 7 SEM images of (**a**) M-CPT (unmilled batch), (**b**) M-CPT (wet-milled batch), (**c**) M-CPT from reproducibility up batch, and (**d**) starting material (MET)

Table 1 Particle size distribution data

Material ID	Note	Particle size (µm)			Span
		D_{10}	D_{50}	D_{90}	
Starting material	MET	41.4	83.8	144	1.2
1012–88-1	M-CPT (unmilled)	600	893	1420	0.9
1012–111-1	M-CPT (milled)	308	461	680	0.8

indicate robust granules, values above 0.6 indicate fragile granules, and a value of 1 indicates no granule integrity (Chan et al. 2013).

Powder mechanics

The performance of M-CPT agglomerates in tableting was evaluated through the construction of compressibility, compactability, tabletability, and manufacturability profiles (Fig. 11). These profiles are generated as per USP < 1062 > requirements and play a crucial role in direct compression as they determine the ability of a powder mixture to be compressed into high-quality tablets. The profiles were generated by subjecting the powder mixture to increasing compression pressures ranging from 50 to 400 MPa. At each pressure point, the physical dimensions and breaking force of the resulting compacts were measured. These properties are critical for ensuring the final tablet product is of consistent quality and can be easily manufactured at scale. The tablets did not exhibit any capping, and increased compression pressures resulted in harder tablets. M-CPT exhibited significantly improved compressibility, tabletability, and compactability characteristics compared to neat MET. The tabletability of M-CPT did not reach a plateau, indicating that further compression of agglomerates was possible. By increasing the particle size of M-CPT and subjecting it to compression pressure, the particles underwent defragmentation, resulting in an increased bonding area and improved tensile strength of the tablets. The ability of a material to reduce its volume under applied pressure is referred to as compressibility. Compressibility is influenced by both

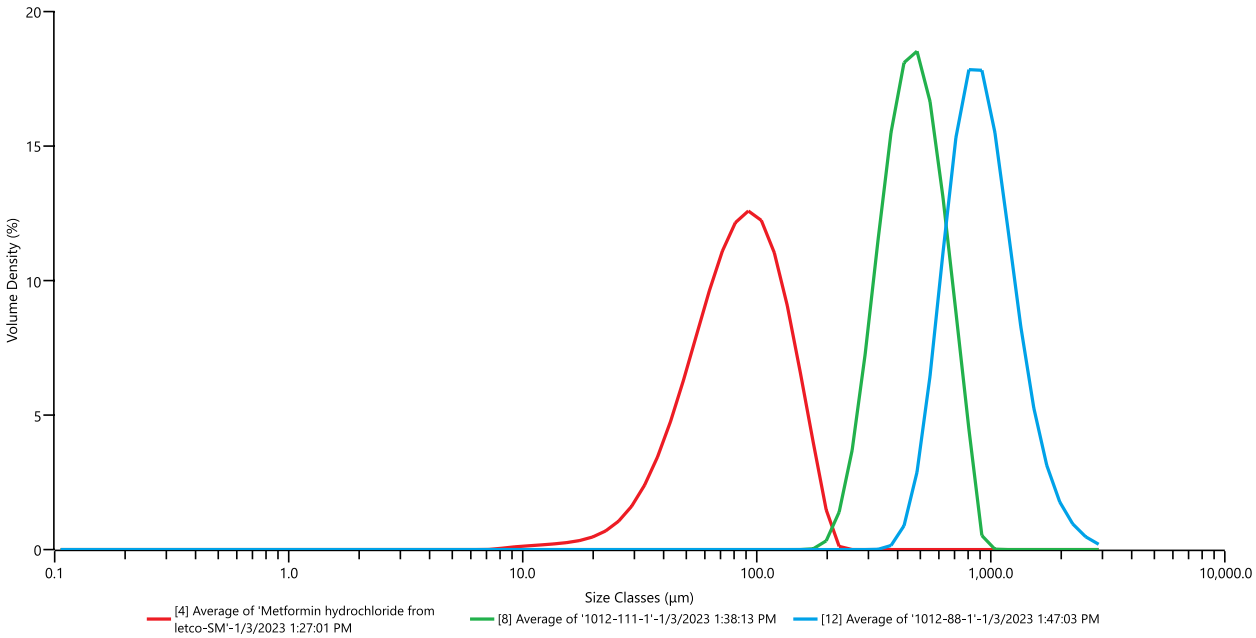


Fig. 8 PSD overlay of (red) starting material (MET), (blue) M-CPT (unmilled batch), and (green) M-CPT (milled batch; from reproducibility batch)

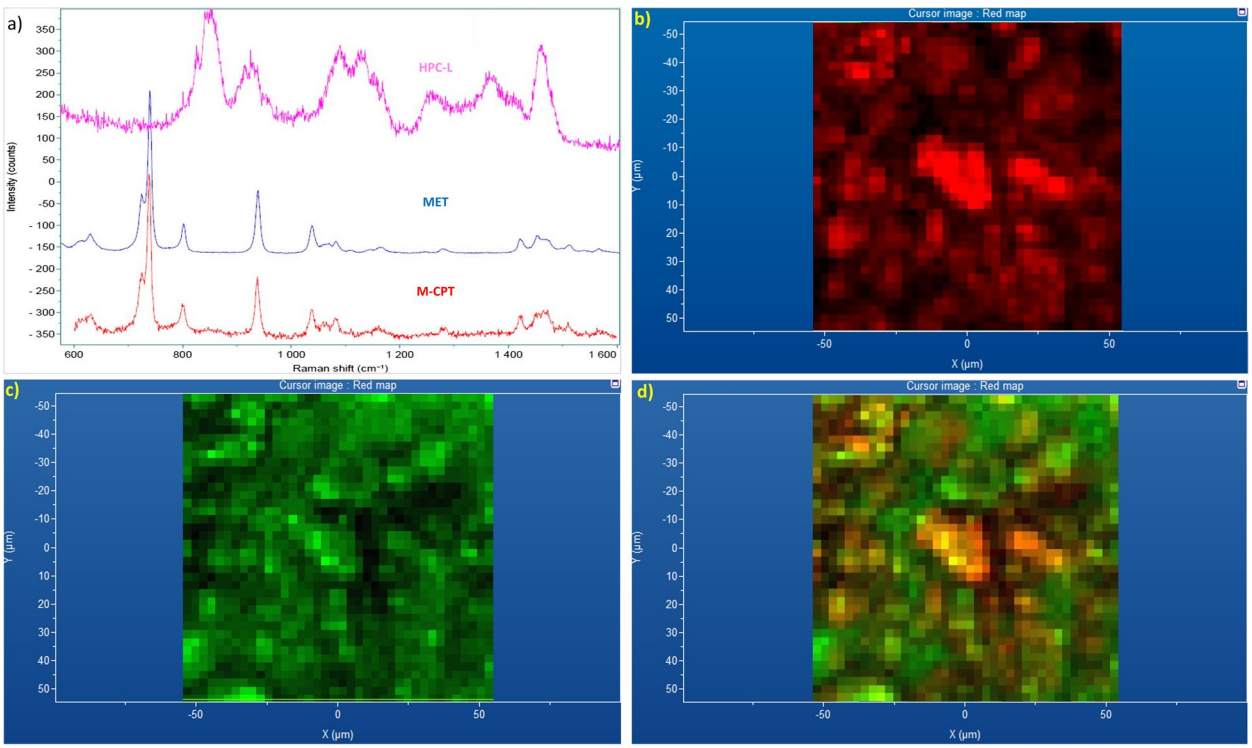


Fig. 9 Spatial drug distribution in M-CPT agglomerates: **a** Raman spectra of HPC-L (pink), MET (blue), and M-CPT agglomerates (red); **b** confocal Raman map of MET; **c** confocal Raman map of HPC-L; and **d** confocal Raman map of M-CPT agglomerates

the mechanical and particulate properties of the material. In the case of M-CPT, increasing the particle size led to particle fragmentation or deformation at lower pressures, which rapidly eliminated pores and resulted in high compressibility. This was attributed to the generation of new bonding areas. However, the compressibility plot showed

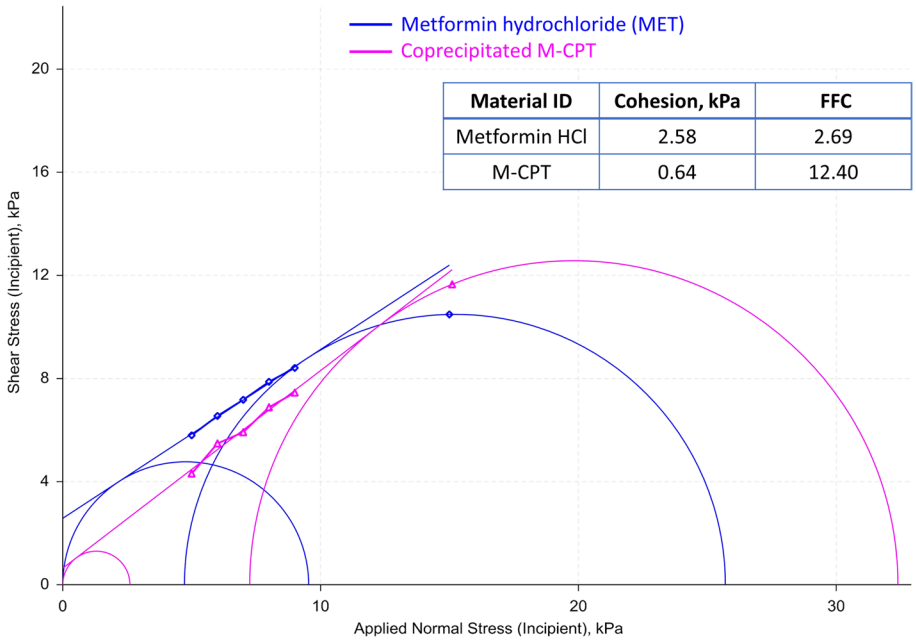


Fig. 10 Incipient shear stress of powder flow as a function of the applied normal stress for neat MET (blue) and coprecipitation generated M-CPT (pink)

Table 2 Granule integrity test results

Granule size range (μm)	Initial (wt%)	%wt after mixing at 73G	GIT index
> 1410	4.26	3.95	0.02
595–1410	6.77	6.44	
250–595	20.6	20.4	
105–250	0.66	0.60	

that the material reached its maximum compressibility at a value exceeding 300 MPa (Chaturvedi et al. 2018). In summary, the improved tabletability of M-CPT compared to neat MET was attributed to its ability to be further compressed due to agglomerate characteristics and the generation of new bonding areas. This led to enhanced tablet tensile strength and reduced tablet porosity.

In the context of "In-Die" Heckel analysis, the yield pressure and plastic deformation are interrelated parameters that provide valuable insights into the behavior of powders during compaction (Sonnergaard 1999). The yield pressure of the M-CPT agglomerates, as determined by Heckel analysis, was found to be 61.8 MPa (Fig. 12). This value suggests that the powder can undergo significant plastic flow when subjected to compression forces and has a low resistance to deformation. The relationship between yield pressure and plastic deformation is intricate yet interconnected. Generally, lower yield pressure tends to exhibit a higher degree of plastic deformation. This implies that the individual particles have a greater tendency to undergo permanent changes in shape or rearrangements within the compact. Such plastic deformation contributes to densification and can enhance the strength of the resulting tablets (Vreeman and Sun 2021). The Styl'One machine simulated the Korsch XL400 rotary press by compressing a formulation containing 100% CPT material at 47 rpm (= 98,700 tablets/h, upper punch speed ~ 70 mm/s) using main compressions of 200 MPa. The resulting tablets exhibited an average tensile strength of 2 MPa ± 0.1 (SD), as well as standard deviations for tablet weight, thickness, and hardness that were well within the range of ± 0.1 (SD). The successful simulation demonstrated the possibility of achieving a production rate of 98,700 tablets/h when compressing CPT material at production speeds.

Drug loading and in vitro dissolution analysis

In coprecipitation, polymer was precipitated from a solution, resulting in a material that contains the coprecipitated substances. Determining the drug loading in coprecipitated material is crucial for controlling dosage, understanding drug interactions, and optimizing formulation and manufacturing processes. To perform drug loading analysis using HPLC, a sample of the drug formulation was first prepared and then injected into the HPLC column. The HPLC system was then used to separate the different components of the sample. The drug compound of interest was identified based on its retention time and

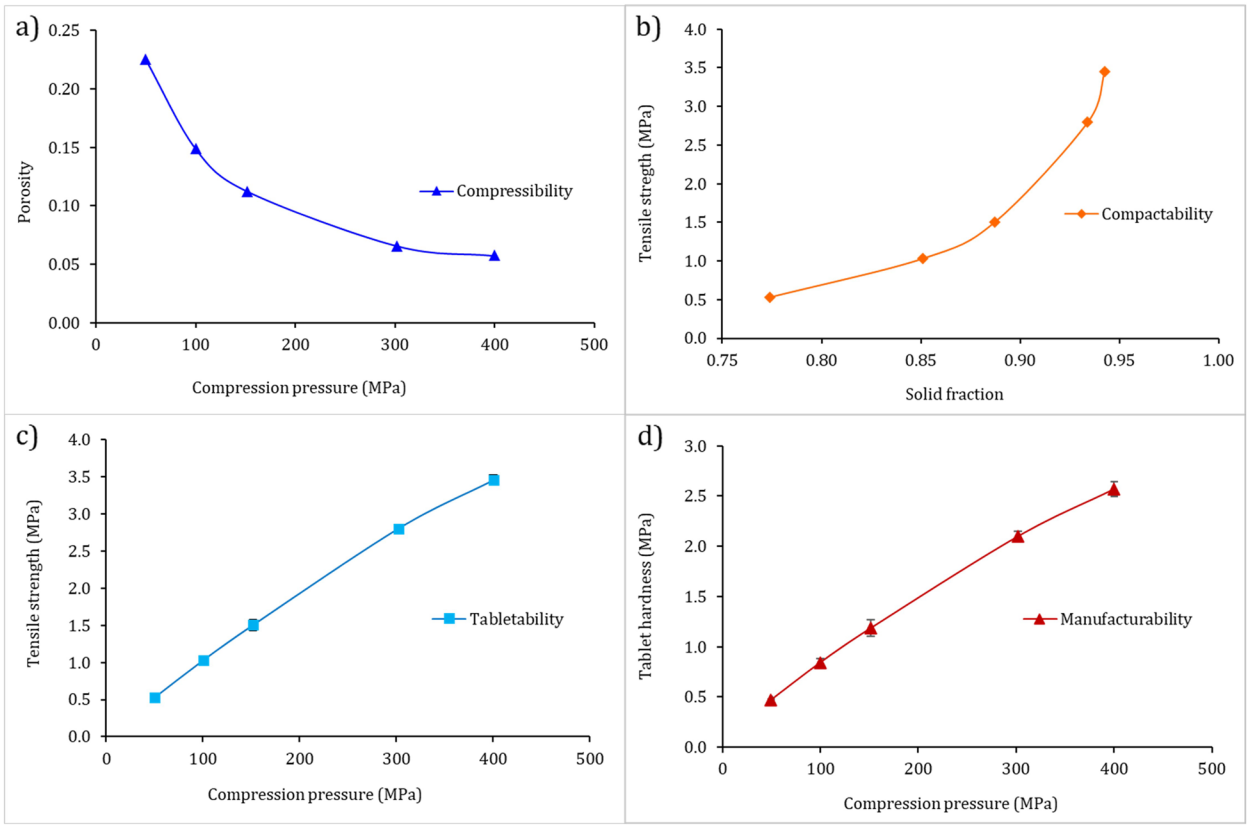


Fig. 11 M-CPT agglomerates: **a** compressibility, **b** compactability, **c** tabletability, and **d** manufacturability profiles

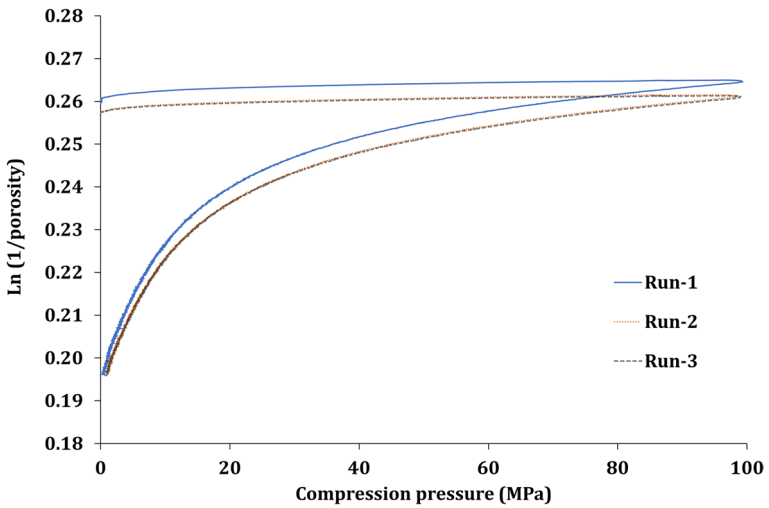


Fig. 12 "In-die" Heckel profile of M-CPT

its corresponding peak area was recorded. The amount of drug in the sample was then determined by comparing the peak area to a standard curve that was generated using known concentrations of the drug. Based on the HPLC analysis, tested M-CPT materials from all batches showed a drug loading of over 78 wt% of the MET. The amount of drug present in agglomerates is very important for the biopharmaceutical performance and therefore it is imperative that the process should provide agglomerates with the uniform distribution of API within

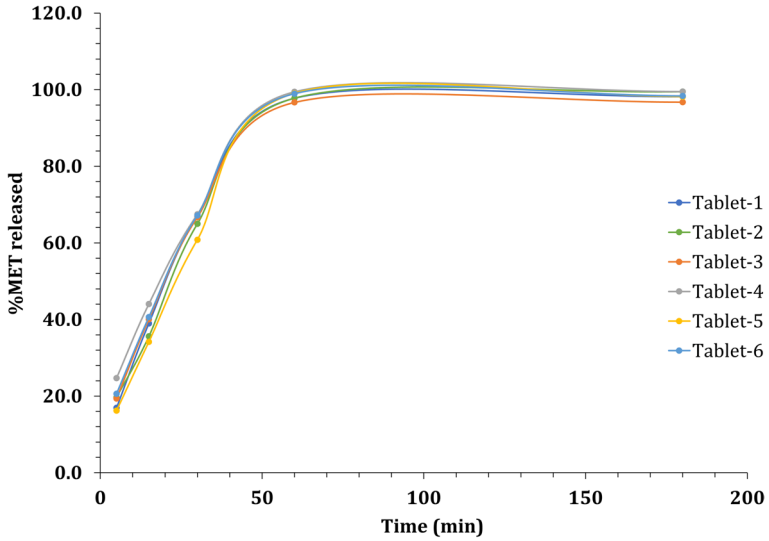


Fig. 13 Dissolution plot of M-CPT from pH 6.8 media

the agglomerates. Based on the HPLC data, agglomerated particles of M-CPT suggest uniform distribution of pure MET within the agglomerates. To ensure that the HPC-L in the M-CPT does not affect the dissolution rate and extent of the drug compared to the available marketed immediate release MET tablets (RLD), it is crucial to match the Q-value in dissolution. The Q-value represents the percentage of drug released over a specified time period and the RLD is used as a reference to establish bioequivalence. Therefore, drug release studies were conducted to determine the release of MET from M-CPT agglomerated particles at pH 6.8. Results showed that the CPT material was able to form an immediate-release tablet dosage form, with over 98% of the drug being released within the first 60 min of the run (Fig. 13). According to the USP 29 and USP 39 standard limit for immediate-release tablet dosage forms, not less than 70% of the labeled amount should be dissolved in 45 min. Based on the available data, it can be concluded that the presence of HPC-L in the M-CPT does not lead to significant changes in the dissolution rate and extent.

Conclusion

The primary objective of using the coprecipitation technique was to create materials with improved powder properties that allow direct compression of high drug loading formulations. In this study, HPC-L, a non-ionic, hydrophilic, and low viscosity excipient, was used to coprocess a poorly compressible API into agglomerated microparticles with improved bulk density and flow properties. The coprecipitation method produced spherical agglomerates with uniform polymer distribution, and solid-state analysis showed no polymorphic changes and residual solvents within the ICH limit. The M-CPT agglomerates showed better flowability compared to neat MET, as revealed by morphological and compositional changes that made them the least cohesive. The presence of the polymer did not significantly alter the drug release profile, demonstrating the suitability of HPC-L for coprecipitation to formulate immediate release dosage form. Large scale production can be challenging as it requires further investigation wherein process parameters such as slurry density, temperature, and milling have to be thoroughly studied and optimize for industrial scale. Overall, this study demonstrates the application of coprocessing with HPC-L as a robust technique for improving powder properties and enabling direct compression formulations for challenging APIs.

Abbreviations

M-CPT	Metformin hydrochloride and HPC-L agglomerates
MET	Metformin hydrochloride
CPT	Coprecipitation
HPC-L	Hydroxypropyl cellulose-L
FFC	Flow function coefficient
BD	Bulk density
TD	Tapped density

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Authors' contributions

KC- conceptualization, methodology, data curation, investigation, formal analysis, writing—original draft preparation. PP, XD- data curation. HS- data curation. VK, SK- supervision, project administration, resources, writing—reviewing and editing.

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Availability of data and materials
Data generated or analyzed during this study are included in this published article. However, some of the data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare that they have no competing interests.

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