

Spherical Crystallisation of Piroxicam–Succinic Acid Multicomponent Particles: Solid-State, Particle, Dissolution and Tableability Characteristics

(Penghabluran Sfera Zarah Pelbagai Komponen Asid Piroksikam–Suksinik: Pencirian Keadaan Pepejal, Zarah, Pelarutan dan Kebolehtabletan)

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ABSTRACT

Piroxicam (PRX) is a poorly water-soluble drug with unfavourable powder properties that may limit dissolution and downstream processing. This study prepared spherical PRX–succinic acid (SUC) multicomponent crystalline particles (Sph-PRX–SUC) by spherical crystallisation and evaluated their solid-state, particle-level, and pharmaceutical properties. PXRD, ATR-FTIR, DSC, TGA, and hot-stage microscopy were complemented by assessments of morphology, particle size, micromeritic properties, wettability, aqueous solubility, intrinsic dissolution, and tableability. Sph-PRX–SUC exhibited a diffraction profile distinct from PRX, SUC, their physical mixture, examined PRX polymorphs, and previously reported PRX–SUC phases, supporting the formation of a distinct PRX–SUC multicomponent crystalline phase. UV–Vis assay showed a PRX content of $75.11 \pm 0.05\%$ w/w across three independently prepared batches. Spherical crystallisation produced rounded millimetre-scale agglomerates with more favourable micromeritic properties and reduced the water contact angle from $92.40 \pm 0.30^\circ$ to $64.80 \pm 0.30^\circ$. Apparent aqueous PRX solubility increased from 0.072 ± 0.016 to 0.312 ± 0.028 mg mL⁻¹, while IDR increased from 0.04634 ± 0.00063 to 0.21252 ± 0.00462 mg cm⁻² min⁻¹. At 200 MPa, tensile strength increased from 0.96 ± 0.16 to 3.54 ± 0.18 MPa. Overall, Sph-PRX–SUC exhibited distinct solid-state and particle characteristics associated with improved dissolution-related and compaction performance.

Keywords: Multicomponent crystalline particles; piroxicam; spherical crystallisation; succinic acid; tableability

ABSTRAK

Piroksikam (PRX) ialah ubat yang sukar larut dalam air dan mempunyai sifat serbuk yang kurang menggalakkan, yang boleh menghadkan prestasi pelarutan dan pemprosesan hiliran. Kajian ini menyediakan zarah kristal multikomponen PRX–asid suksinik (SUC) berbentuk sfera (Sph-PRX–SUC) melalui penghabluran sfera dan menilai sifat keadaan pepejal, ciri zarah serta sifat farmaseutikalnya. PXRD, ATR-FTIR, DSC, TGA dan mikroskopi pentas panas digunakan bersama penilaian morfologi, saiz zarah, sifat mikromeritik, kebolehasahan, keterlarutan akueus, pelarutan intrinsik dan kebolehtabletan. Sph-PRX–SUC menunjukkan profil pembelauan yang berbeza daripada PRX, SUC, campuran fizikalnya, polimorf PRX yang dinilai serta fasa PRX–SUC yang telah dilaporkan, sekali gus menyokong pembentukan fasa kristal multikomponen PRX–SUC yang berbeza. Penentuan kandungan menggunakan UV–Vis menunjukkan kandungan PRX sebanyak $75.11 \pm 0.05\%$ w/w merentas tiga kelompok yang disediakan secara bebas. Penghabluran sfera menghasilkan aglomerat bersaiz milimeter yang membulat dengan sifat mikromeritik yang lebih menggalakkan serta mengurangkan sudut sentuhan air daripada $92.40 \pm 0.30^\circ$ kepada $64.80 \pm 0.30^\circ$. Keterlarutan akueus PRX yang diukur meningkat daripada 0.072 ± 0.016 kepada 0.312 ± 0.028 mg mL⁻¹, manakala kadar pelarutan intrinsik (IDR) meningkat daripada 0.04634 ± 0.00063 kepada 0.21252 ± 0.00462 mg cm⁻² min⁻¹. Pada tekanan mampatan 200 MPa, kekuatan tegangan meningkat daripada 0.96 ± 0.16 kepada 3.54 ± 0.18 MPa. Secara keseluruhan, Sph-PRX–SUC menunjukkan ciri keadaan pepejal dan zarah yang berbeza serta dikaitkan dengan peningkatan prestasi berkaitan pelarutan dan pemampatan.

Kata kunci: Asid suksinik; kebolehtabletan; penghabluran sfera; piroksikam; zarah kristal multikomponen

INTRODUCTION

Poor aqueous solubility remains a major limitation in the development of oral solid dosage forms, particularly

for Biopharmaceutics Classification System class II drugs, where dissolution may limit the rate and extent of absorption (Krishnaiah 2010). Piroxicam (PRX), a non-

steroidal anti-inflammatory drug used for musculoskeletal and joint disorders, is affected by this limitation because of its low aqueous solubility and dissolution-limited performance (Al-Khedairy 2012; Ammanage et al. 2020). In addition, PRX exhibits solid-state complexity, including polymorphic and solvate-related behaviour, making comprehensive solid-state characterisation essential when developing modified crystalline or multicomponent forms (Emami, Siahi-Shadbad & Adibkia 2018; Liu et al. 2019).

Crystal engineering and pharmaceutical multicomponent solids provide a rational route to modify solid-state, dissolution, and mechanical properties without changing the covalent structure of the active pharmaceutical ingredient (Gadade & Pekamwar 2016; Thayyil et al. 2020). Succinic acid (SUC), a dicarboxylic acid coformer, is relevant in this context because carboxylic acid groups can participate in intermolecular interactions with complementary functional groups in drug molecules (Ameerah et al. 2023; Singh et al. 2023). Succinic-acid-based multicomponent systems have been reported for several drugs, including carbamazepine (Majeed et al. 2017), loratadine (Setyawan et al. 2021), piperine (Erizal et al. 2020a), and meloxicam (Ogienko et al. 2018), with system-dependent improvements in solubility, dissolution, or solid-state performance.

The PRX–SUC system has been investigated previously. Liu et al. (2019) reported an acetonitrile-solvated PRX–SUC cocrystal and distinguished solvated and nonsolvated PRX–SUC forms using crystallographic and vibrational evidence. Emami, Siahi-Shadbad and Adibkia (2018) also included previously reported PRX–SUC cocrystal data in evaluating dissolution-

related properties of PRX cocrystals. These studies established the solid-state relevance of the PRX–SUC pair, but they were not primarily designed to engineer spherical PRX–SUC particles or to integrate assessments of powder flow, wettability, dissolution, and tabletability.

Spherical crystallisation is a particle-engineering strategy that converts fine crystals into larger agglomerates during crystallisation (Figure 1), thereby modifying particle size, shape, packing, flowability, and compaction-related behaviour (Kawashima 1987; Pitt et al. 2018). When multicomponent solid formation occurs during spherical crystallisation, changes in both solid-state and particle-level characteristics may be obtained within the same process. Previous studies have reported favourable powder and dissolution properties for spherical multicomponent drug systems (Chen et al. 2019). However, comprehensive evaluation of spherical PRX–SUC systems remains limited, particularly across solid-state characteristics, morphology, particle-size distribution, micromeritics, wettability, aqueous solubility, dissolution, and tabletability.

This study therefore aimed to prepare spherical PRX–SUC multicomponent particles by spherical crystallisation and to characterise their solid-state, particle-level, and pharmaceutical properties. The product was compared with untreated PRX, SUC, and their physical mixture for solid-state characterisation, while selected functional properties were evaluated relative to untreated PRX. The study was designed to determine the overall characteristics of the processed spherical PRX–SUC system rather than to quantitatively separate the individual contributions of the coformer, solid-state transformation, and particle-level modification.

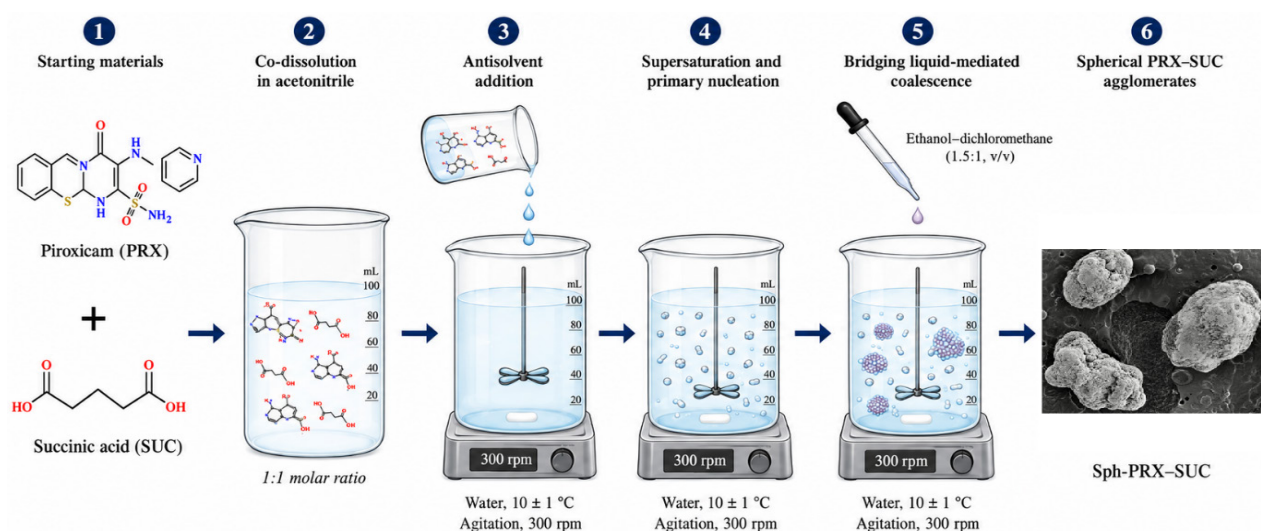


FIGURE 1. Schematic illustration of the formation of spherical PRX–SUC particles by spherical crystallisation

MATERIALS AND METHODS

MATERIALS

Piroxicam (PRX; assay 99.45%) was obtained from Nantong Jinghua Pharmaceutical Co., Ltd. (China). Succinic acid (SUC; purity $\geq 99\%$) was purchased from Merck and used as received. Analytical-grade acetonitrile, dichloromethane, and absolute ethanol ($\geq 99.9\%$) were obtained from Merck KGaA (Darmstadt, Germany). Demineralised water was used as the antisolvent and aqueous medium.

PREPARATION OF PHYSICAL MIXTURE AND SPHERICAL PRX–SUC PARTICLES

The physical mixture (PM) was prepared by dry mixing equimolar amounts of PRX and SUC until a visually homogeneous powder was obtained. No solvent was used, and the mixture was stored in a desiccator before characterisation. Spherical PRX–SUC particles (Sph-PRX–SUC) were prepared by one-step spherical crystallisation. PRX (0.5000 g, 1.511 mmol) and SUC (0.1771 g, 1.501 mmol) were co-dissolved in 20 mL of acetonitrile under magnetic stirring and sonicated for 5 min. The solution was added dropwise at approximately $1\text{--}2\text{ mL min}^{-1}$ into 70 mL of demineralised water maintained at $10 \pm 1\text{ }^{\circ}\text{C}$ and mechanically agitated at 300 rpm. After nucleation, 5 mL of ethanol–dichloromethane (1.5:1, v/v) was added dropwise as the bridging liquid, and the mixture was agitated for 30 min. The particles were collected by vacuum filtration, dried at $40\text{ }^{\circ}\text{C}$ for 30 min, and stored in a vacuum desiccator over silica gel for 48 h at room temperature. The dried product from each independently prepared batch was weighed, and isolated product recovery (%) was calculated relative to the total initial mass of PRX and SUC (0.6771 g).

DETERMINATION OF PRX CONTENT IN Sph-PRX–SUC

The PRX content of Sph-PRX–SUC was determined by UV–Vis spectrophotometry in methanol. PRX calibration standards ($2\text{--}20\text{ }\mu\text{g mL}^{-1}$) were measured at 356 nm in triplicate. Potential SUC interference was assessed using pure SUC solutions at corresponding concentrations. Accuracy was evaluated by recovery studies using 1:1 molar PRX:SUC physical mixtures at 80, 100, and 120% of the target PRX concentration. For product assay, approximately 25 mg of Sph-PRX–SUC was dissolved in methanol and serially diluted within the calibration range. Three independently prepared batches were analysed in triplicate, and PRX content was expressed as % w/w based on the calibration curve.

POWDER X-RAY DIFFRACTION

Powder X-ray diffraction (PXRD) was performed to evaluate crystallographic differences among PRX, SUC,

PM, and Sph-PRX–SUC. Diffractograms were recorded using a D8 Advance diffractometer (Bruker, Karlsruhe, Germany) with Cu K α radiation ($\lambda = 1.5406\text{ }\text{\AA}$). Samples were gently packed into a zero-background silicon holder and levelled with a glass slide to minimise preferred orientation. Patterns were collected over $5\text{--}40^{\circ}$ 2θ with a step size of 0.02° and a scan rate of $2^{\circ}\text{ min}^{-1}$ at ambient temperature.

For phase comparison, simulated PXRD patterns of reported PRX polymorphs and PRX–SUC phases were generated from crystallographic structures obtained from the Cambridge Structural Database (CSD) and compared with the experimental Sph-PRX–SUC pattern over $5\text{--}40^{\circ}$ 2θ using Cu K α radiation ($\lambda = 1.5406\text{ }\text{\AA}$). PRX Forms I–III were represented by BIYSEH01, BIYSEH02, and BIYSEH07, respectively.

ATR-FTIR SPECTROSCOPY

ATR-FTIR spectra were recorded using an Agilent Cary 630 FTIR spectrometer (Agilent Technologies, Santa Clara, CA, USA) to assess changes in the molecular environment of PRX and SUC. Spectra were collected over $4000\text{--}650\text{ cm}^{-1}$ at a resolution of 4 cm^{-1} using 32 scans per sample. Band shifts, broadening, and changes in intensity were interpreted as evidence of changes in the local molecular environment.

DIFFERENTIAL SCANNING CALORIMETRY

Differential scanning calorimetry (DSC) was performed using a DSC 4000 differential scanning calorimeter (PerkinElmer, Waltham, MA, USA). Approximately 3–5 mg of each sample was sealed in an aluminium pan and heated from $30\text{ to }300\text{ }^{\circ}\text{C}$ at $10\text{ }^{\circ}\text{C min}^{-1}$ under nitrogen purge at 20 mL min^{-1} . Temperature and enthalpy calibration were performed using indium. Thermograms were analysed using PerkinElmer Pyris software.

THERMOGRAVIMETRIC ANALYSIS

Thermogravimetric analysis (TGA) was performed using a TGA 8000 analyser (PerkinElmer). Approximately 3–5 mg of sample was heated from $30\text{ to }500\text{ }^{\circ}\text{C}$ at $10\text{ }^{\circ}\text{C min}^{-1}$ under nitrogen purge at 20 mL min^{-1} . Mass-loss profiles were used to screen for possible volatile loss, retention of solvent or water, and thermal degradation behaviour.

HOT-STAGE MICROSCOPY

Thermal morphological changes were observed using a hot-stage microscopy setup consisting of a Dline hot stage (Indonesia), a polarising microscope (China), and a Touptek microscope camera (China). Samples were placed on glass slides and heated manually to selected temperatures near and above the components' thermal transition ranges. Images were recorded at the

temperatures indicated in the micrographs at a total optical magnification of 40 $\times$. Because the heating rate was manually controlled and not quantitatively calibrated, HSM was used only as a qualitative supporting technique.

SCANNING ELECTRON MICROSCOPY

Particle morphology and surface texture were examined using a SU8010 field-emission scanning electron microscope (Hitachi, Tokyo, Japan). Powder samples were mounted on aluminium stubs using double-sided carbon tape and sputter-coated with gold under vacuum. Micrographs were acquired at accelerating voltages of 5–10 kV at selected magnifications to compare untreated PRX and Sph-PRX–SUC.

PARTICLE-SIZE AND MORPHOLOGY ANALYSIS

Particle-size distribution of Sph-PRX–SUC was determined by static image analysis. Digital images were acquired using an EOS 90D camera (Canon, Tokyo, Japan) under standardised illumination and a fixed working distance. Spatial calibration was established in ImageJ using a millimetre ruler included in a reference image acquired under the same imaging conditions. The resulting pixel-to-length calibration was applied to particle images acquired using the same camera settings and working distance. At least 150 particles from at least three independent fields of view were analysed using ImageJ software (NIH, Bethesda, MD, USA). Feret diameter and particle-length distribution were used to describe the size distribution of the agglomerates.

MICROMERITIC PROPERTIES

Bulk powder properties of PRX and Sph-PRX–SUC were evaluated to compare powder-flow behaviour. Bulk and tapped densities were determined using a JV 2000 tap density tester (Copley Scientific, Nottingham, UK). Hausner ratio and Carr's compressibility index were calculated separately for each replicate from the corresponding bulk and tapped densities according to $HR = \rho_{\text{tapped}}/\rho_{\text{bulk}}$ and $CI = [(\rho_{\text{tapped}} - \rho_{\text{bulk}})/\rho_{\text{tapped}}] \times 100$, respectively. The angle of repose was measured using the fixed-funnel method with an automated powder flow analyser (PTG-S4, Pharma Test, Hainburg, Germany). Flow rate was also measured. Measurements were performed in triplicate.

WETTABILITY

Surface wettability was measured by the sessile drop method. Flat-faced compacts of PRX and Sph-PRX–SUC were prepared at 195.1 MPa, corresponding to 1 metric ton applied with an 8 mm flat-faced punch. Static contact angles were measured using a DSA25 drop shape analyser (Krüss GmbH, Hamburg, Germany). A 3 μL

droplet of deionised water was deposited onto the compact surface, and the initial contact angle was recorded immediately using the instrument's image-analysis software. Measurements were performed in triplicate and reported as mean $\pm$ SD.

AQUEOUS SOLUBILITY STUDY

Aqueous solubility was determined by adding 10 mg of each sample to 10 mL of demineralised water. Suspensions were stirred at 300 rpm for 24 h at room temperature and filtered through a 0.45 μm membrane filter. PRX concentrations in the filtrates were determined directly by UV–Vis spectrophotometry (Agilent Cary 60) against a PRX calibration curve prepared in the same medium. For Sph-PRX–SUC, the results were expressed as apparent aqueous PRX solubility (mg mL^{-1}). Measurements were performed in triplicate and reported as mean $\pm$ SD.

INTRINSIC DISSOLUTION STUDY

Intrinsic dissolution behaviour was evaluated using a paddle-over-stationary-disc configuration with USP Apparatus 2 (708-DS, Agilent Technologies, Santa Clara, CA, USA). Powder samples were compressed at 195.1 MPa using an 8 mm flat-faced punch for 1 min. Each compact was retained in a holder so that only one circular face, corresponding to a nominal exposed area of 0.50 cm^2 , was in contact with the dissolution medium. Dissolution testing was performed in 900 mL of phosphate buffer pH 6.8 at 37 ± 0.5 $^{\circ}\text{C}$ with paddle rotation at 50 rpm. At predetermined intervals, 5 mL aliquots were withdrawn, filtered through a 0.45 μm PVDF membrane, and replaced with an equal volume of pre-warmed medium. PRX concentrations were determined directly using a UV–Vis spectrophotometer (Agilent Cary 60). Cumulative dissolved PRX was corrected for sampling and normalised to the exposed compact area. IDR was calculated separately for each replicate from the slope of the linear portion of cumulative dissolved PRX per unit area versus time over 5–60 min, with linearity accepted at $r^2 \geq 0.99$. The resulting IDR values were expressed as mean $\pm$ SD ($n = 3$). Compact integrity was visually monitored throughout the 60-min test; no cracking, fragmentation, or edge loss was observed, although a gradual reduction in compact thickness occurred as dissolution proceeded.

TABLETABILITY AND TENSILE STRENGTH

Tabletability profiles of PRX and Sph-PRX–SUC were obtained by compacting 200 mg powder aliquots into flat-faced cylindrical tablets using a Carver 3851-0 hydraulic laboratory press (Carver Inc., Wabash, IN, USA) equipped with 8 mm flat-faced punches. Compression pressures were set at 50, 100, 150, and 200 MPa with a dwell time of approximately 5–10 s. The compacts

were stored at 25 ± 2 °C and 40-60% relative humidity for 24 h before testing. Diametral breaking force and tablet thickness were measured using a TBH 220 W automated hardness tester (ERWEKA GmbH, Langen, Germany). Tablet tensile strength (σ_t) was calculated as:

$$\sigma_t = \frac{2F}{\pi Dt}$$

where F is the diametral breaking force; D is the tablet diameter; and t is the tablet thickness. Measurements were performed in triplicate and reported as mean $\pm$ SD.

DATA AND STATISTICAL ANALYSIS

Quantitative measurements were performed in triplicate unless otherwise stated and are presented as mean $\pm$ SD. Pairwise comparisons between untreated PRX and Sph-PRX-SUC for aqueous solubility and IDR were performed using two-sided Welch's t-tests without assuming equal variances. IDR values were calculated independently from the linear regression slope of each dissolution replicate. Tensile strengths were compared between the two samples at each compression pressure using Welch's t-tests, with Holm adjustment for the four pressure-specific comparisons. Statistical significance was set at $p < 0.05$. Other physicochemical and micromeritic measurements were evaluated descriptively.

RESULT AND DISCUSSION

FORMATION OF Sph-PRX-SUC PARTICLES

Spherical crystallisation produced a PRX-SUC solid with a visibly distinct particle habit from that of untreated PRX, hereafter denoted as Sph-PRX-SUC. The term 'spherical' refers specifically to the agglomerated particle morphology generated during processing and does not imply a particular crystallographic identity or phase purity. Across three independently prepared batches, the isolated product recovery was $52.98 \pm 1.57\%$. Solid-state transformation was subsequently evaluated using PXRD, ATR-FTIR, DSC, TGA, and hot-stage microscopy, whereas SEM and particle-size analysis were used to assess the particle-level characteristics.

PRX CONTENT OF ISOLATED Sph-PRX-SUC

The UV-Vis assay was linear over 2-20 $\mu\text{g mL}^{-1}$ ($A = 0.051156C + 0.002419$; $R^2 = 0.999999$), while SUC showed negligible absorbance at 356 nm, indicating minimal interference with PRX determination. Recovery from 1:1 molar PRX:SUC physical mixtures ranged from 99.85 to 100.18%. The PRX contents of three independently prepared Sph-PRX-SUC batches were 75.05 ± 0.04 , 75.14 ± 0.12 , and $75.14 \pm 0.05\%$ w/w,

respectively, giving a mean PRX content of $75.11 \pm 0.05\%$ w/w ($n = 3$ batches). This value was close to the theoretical PRX mass fraction of 73.73% expected for an equimolar PRX:SUC binary composition. However, because SUC was not quantified independently, the assay indicates a composition close to the nominal equimolar system but does not establish an exact 1:1 stoichiometry.

PXRD ANALYSIS

PXRD was used to evaluate the solid-state characteristics of PRX, SUC, PM, and Sph-PRX-SUC (Figure 2). Experimental PRX showed major reflections at approximately 8.60, 14.48, 17.66, 21.72, and 27.38° 2 θ , closely corresponding to the simulated pattern of PRX Form I (BIYSEH01). The PM retained the principal reflections of PRX and SUC, consistent with a physical superposition of the parent components and supporting its use as a control for process-induced solid-state changes (Garbacz & Wesolowski 2018; Wiscons & Matzger 2017). In contrast, Sph-PRX-SUC exhibited a non-superimposable pattern with characteristic reflections at approximately 11.98, 18.46, 19.04, 19.50, 21.40, 22.54, 26.30, and 28.22° 2 θ .

To further assess phase identity, the experimental Sph-PRX-SUC pattern was compared with simulated PXRD patterns of PRX Forms I-III (BIYSEH01, BIYSEH02, and BIYSEH07), the reported nonsolvated PRX-SUC phase, and the PRX-SUC acetonitrile solvate (Figure 2(B)). The latter comparison was particularly relevant because acetonitrile-solvated and nonsolvated PRX-SUC forms have previously been reported and distinguished crystallographically (Liu et al. 2019). Sph-PRX-SUC did not reproduce the overall diffraction pattern or prominent diagnostic reflections of any of these reference phases. Notably, the intense low-angle reflection characteristic of the simulated PRX-SUC acetonitrile solvate was absent from the experimental product pattern.

The distinct diffraction profile therefore supports a solid-state transformation beyond simple physical mixing or polymorphic conversion of PRX alone (Qiao et al. 2017). Together with the lack of full-pattern agreement with the examined PRX polymorphs and previously reported PRX-SUC phases, the PXRD results support the formation of a distinct PRX-SUC multicomponent crystalline phase under the spherical crystallisation conditions used in this study.

FTIR ANALYSIS

ATR-FTIR spectra of PRX, SUC, PM, and Sph-PRX-SUC are shown in Figure 3. The PM largely retained the characteristic bands of both PRX and SUC, consistent with a physical superposition of the parent components. In contrast, Sph-PRX-SUC showed clear

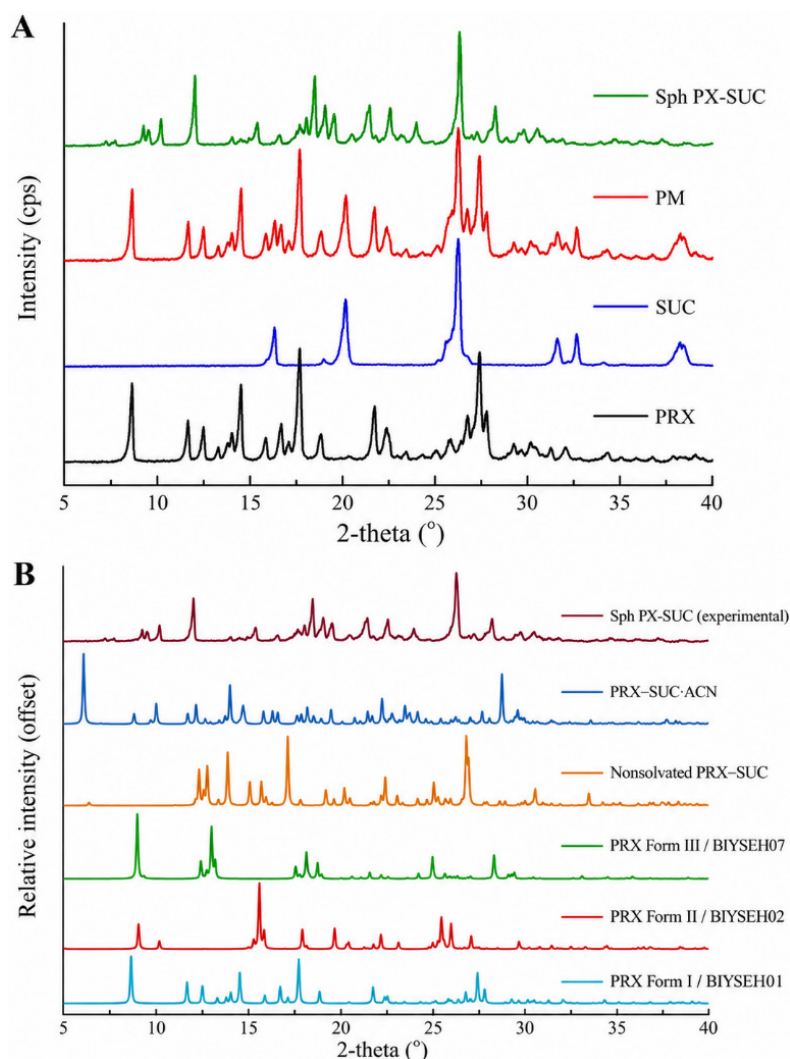


FIGURE 2. PXRD analysis of PRX-SUC systems. (A) Experimental PXRD patterns of PRX, SUC, PM, and Sph-PRX-SUC recorded over 5–40° 2 θ . (B) Comparison of the experimental Sph-PRX-SUC pattern with simulated powder diffraction patterns of PRX Form I (BIYSEH01), PRX Form II (BIYSEH02), PRX Form III (BIYSEH07), the reported nonsolvated PRX-SUC phase, and the PRX-SUC acetonitrile solvate

spectral changes, particularly in the hydrogen-bond-sensitive and carbonyl regions. The PRX band near 3334 cm^{-1} was broadened and shifted, while the characteristic PRX and SUC carbonyl-related bands around 1625 and 1677 cm^{-1} were reorganised into new features at approximately 1634, 1595, and 1521 cm^{-1} . Additional changes were observed in the fingerprint region, including shifts and band reorganisation between approximately 1400 and 1000 cm^{-1} . These spectral changes indicate altered local environments of PRX and SUC functional groups and are consistent with intermolecular interactions in the transformed multicomponent solid (Panzade et al. 2017).

Overall, the FTIR profile of Sph-PRX-SUC differed from that of the physical mixture and therefore

supports the PXRD evidence of solid-state transformation. However, FTIR provides only complementary evidence and cannot independently establish phase purity, exact stoichiometry, molecular packing, or a specific hydrogen-bond synthon. The spectra were therefore interpreted together with PXRD and thermal analyses rather than as standalone evidence of cocrystal formation (Qiao et al. 2017).

THERMAL BEHAVIOUR: DSC, TGA, AND HSM

DSC, TGA, and HSM were used to evaluate whether Sph-PRX-SUC exhibited thermal behaviour distinct from that of PRX, SUC, and PM (Figure 4). DSC of pure PRX showed a dominant endothermic event at approximately

196.6 °C, whereas SUC exhibited a strong endothermic transition at approximately 185.1 °C (Figure 4(A)). The PM thermogram retained overlapping thermal features near approximately 186.2 and 197.4 °C, indicating that the physical mixture largely preserved the individual thermal responses of PRX and SUC. In contrast, Sph-PRX–SUC showed a broad low-temperature event centred at approximately 135.4 °C and a dominant high-temperature transition at approximately 196.8 °C. The absence of a clearly resolved SUC-like endotherm in Sph-PRX–SUC suggests a thermal response distinct from that of simple physical mixing. However, because the dominant high-temperature transition occurred close to the main PRX endotherm, this event should not be assigned solely to a newly formed cocrystal phase without additional structural confirmation. DSC therefore supports solid-state transformation but remains complementary to PXRD and FTIR, particularly because eutectic melting, recrystallisation, desolvation, polymorphic transformation, and degradation may complicate thermal interpretation in multicomponent pharmaceutical solids (Healy et al. 2017).

TGA showed that Sph-PRX–SUC retained 98.12% and 97.35% of its mass at 150 and 200 °C, respectively (Figure 4(B)). Thus, the broad DSC event near 135.4 °C was not associated with substantial mass loss, arguing against major dehydration or desolvation. This is also

inconsistent with the reported PRX–SUC acetonitrile solvate, for which the stoichiometric ACN content would be approximately 5.4 wt%. Together with the PXRD mismatch in Figure 2(B), the low mass loss up to 150 °C argues against Sph-PRX–SUC being predominantly the reported acetonitrile-solvated phase. The main degradation occurred at higher temperatures, with 50% residual mass reached at approximately 299.6 °C, compared with 389.3 and 342.5 °C for PRX and PM, respectively. These results indicate a distinct thermal degradation profile rather than improved high-temperature stability (Healy et al. 2017; Liu et al. 2019).

HSM provided qualitative visual support for DSC observations (Figure 4(C)). PRX remained as dispersed particles at 148 °C and showed extensive fusion or droplet formation at 235 °C, whereas SUC showed crystalline fragments at 113 °C and marked morphological changes at 203 °C. Sph-PRX–SUC retained agglomerated particulate features at 117 °C and showed partial fusion into droplet-like domains at 208 °C, indicating a thermal evolution that differed from the starting materials. Because the HSM heating rate was manually controlled, these observations are interpreted only as supportive evidence of thermal morphological change, not as independent confirmation of cocrystal formation (Kumar, Singh & Nanda 2020).

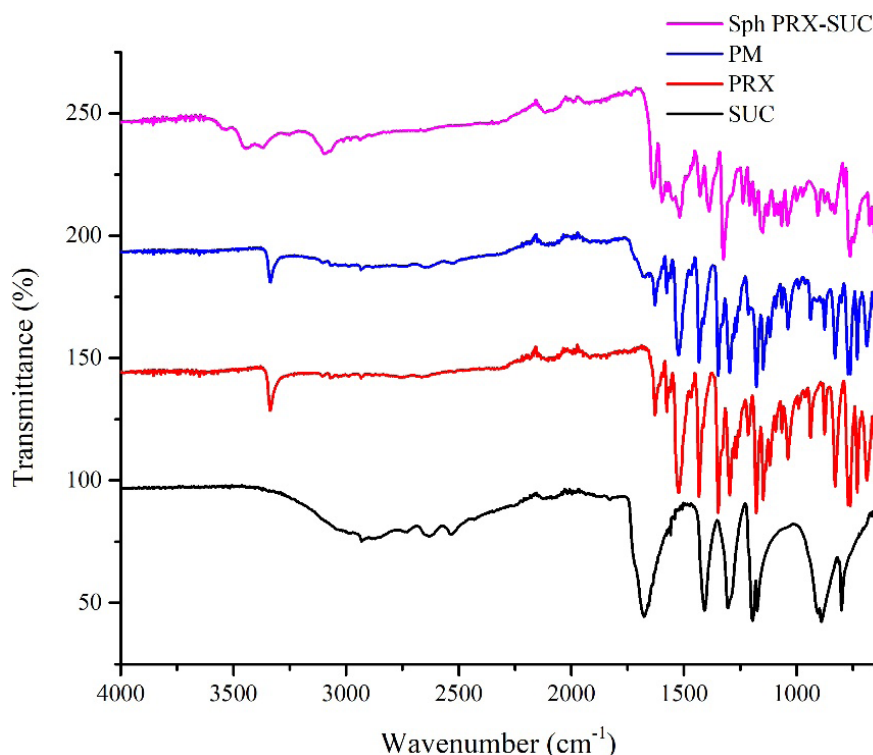


FIGURE 3. ATR-FTIR spectra of PRX, SUC, PM, and Sph-PRX–SUC collected over the range of 4000–650 cm^{-1}

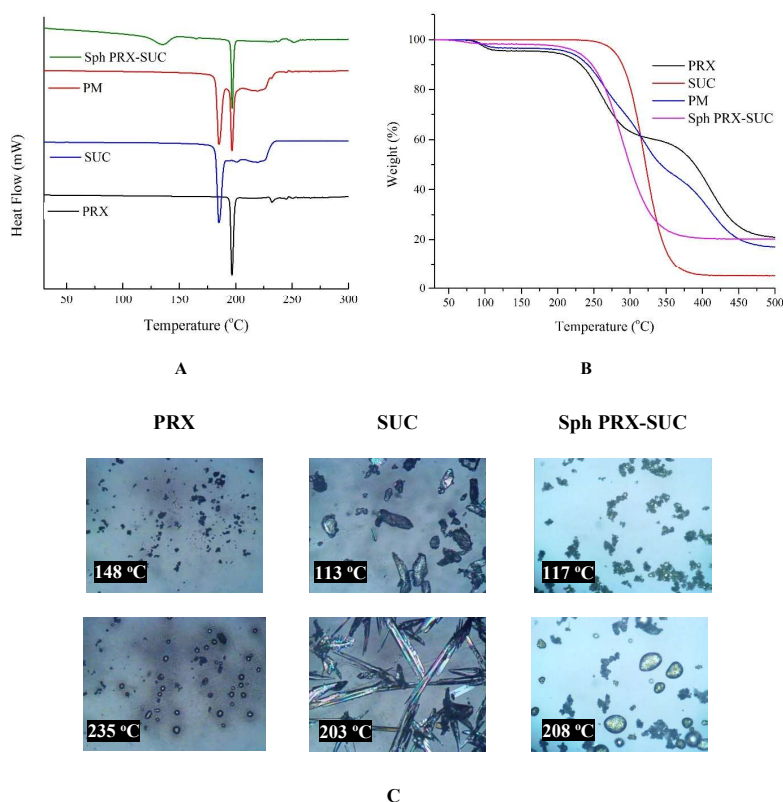


FIGURE 4. Thermal analysis of PRX, SUC, PM, and Sph-PRX-SUC: (A) DSC thermograms, (B) TGA profiles, and (C) representative hot-stage microscopy images acquired at selected temperatures at $40\times$ total magnification

MORPHOLOGY AND PARTICLE-SIZE DISTRIBUTION

SEM showed clear morphological differences between untreated PRX and Sph-PRX-SUC (Figure 5(A), 5(B)). PRX consisted of irregular angular fragments, whereas Sph-PRX-SUC formed rounded-to-ellipsoidal agglomerates with rough compact surfaces. SEM was used for qualitative assessment of morphology and surface texture, whereas quantitative particle size was determined independently from ruler-calibrated low-magnification images covering a larger particle population.

Image analysis of 156 particles showed a unimodal distribution with a mean particle length of 1.584 ± 0.399 mm, a median of 1.537 mm, and D10 and D90 values of 1.067 and 2.182 mm, respectively (Figure 5(C)). Most particles were distributed between approximately 1.2 and 1.8 mm, confirming the predominance of millimetre-scale agglomerates. The SEM field therefore represents selected particles for morphological observation rather than the full particle-size population.

These particle-level differences were accompanied by changes in micromeritic and compaction properties. However, the relatively large agglomerate size may require further size control during downstream formulation to minimise potential blend- and content-uniformity issues (Pitt et al. 2018).

The relatively large agglomerate size may require further size classification or controlled milling before downstream tablet formulation, particularly where blend and content uniformity are critical. However, extensive milling could partially diminish the morphology-related handling advantages of the spherical agglomerates. Therefore, downstream size optimisation should balance particle-size control against preservation of the favourable powder properties observed in the present study.

MICROMERITIC PROPERTIES

Sph-PRX-SUC showed markedly different micromeritic behaviour from untreated PRX (Table 1). The angle of repose decreased from $42.56 \pm 1.75^\circ$ for PRX to $32.86 \pm 1.06^\circ$ for Sph-PRX-SUC, while the flow rate increased from 0.162 ± 0.005 to 1.62 ± 0.17 g s⁻¹. Consistent differences were observed in the density-derived indices: the Hausner ratio decreased from 2.11 ± 0.04 to 1.23 ± 0.03 , and Carr's compressibility index decreased from $52.52 \pm 0.81\%$ to $18.98 \pm 1.78\%$.

Bulk density increased from 0.310 ± 0.005 to 0.390 ± 0.009 g mL⁻¹, whereas tapped density decreased from 0.652 ± 0.011 to 0.482 ± 0.019 g mL⁻¹, indicating substantially less volume change upon tapping for Sph-PRX-SUC. Although the angle of repose of untreated PRX suggested passable gravitational flow, its

markedly higher Hausner ratio and Carr's index indicated pronounced consolidation under tapping. This apparent discrepancy reflects the different aspects of powder behaviour assessed by static pile formation and density-based indices and highlights the importance of considering multiple flow parameters.

Overall, the lower angle of repose, Hausner ratio, and Carr's index together with the approximately tenfold higher flow rate demonstrate more favourable micromeritic behaviour for Sph-PRX-SUC than for untreated PRX. These differences occurred alongside the rounded agglomerated morphology observed by SEM (Indra, Nur'aini & Pratita 2026); however, the present design does not permit the individual contribution of particle morphology to be separated from accompanying compositional and solid-state differences.

WETTABILITY, SOLUBILITY, AND DISSOLUTION PERFORMANCE

Wettability was evaluated to assess liquid–solid interaction at the compact surface (Figure 6(A)). Untreated PRX showed a contact angle of $92.40 \pm 0.30^\circ$, whereas Sph-PRX-SUC showed a lower value of $64.80 \pm 0.30^\circ$, corresponding to an absolute decrease of 27.6° . The lower contact angle indicates improved wettability of the processed material. Because lower contact angles

are generally associated with more favourable liquid spreading and medium penetration, this observation is consistent with, but does not independently explain, the higher dissolution observed for Sph-PRX-SUC (Lu et al. 2014).

Apparent aqueous PRX solubility was higher for Sph-PRX-SUC than for untreated PRX (Figure 6(B)). PRX concentrations were determined directly by UV–Vis spectrophotometry against the PRX calibration curve, without correction based on an assumed PRX:SUC stoichiometric ratio. Untreated PRX showed a solubility of $0.072 \pm 0.016 \text{ mg mL}^{-1}$, whereas Sph-PRX-SUC reached $0.312 \pm 0.028 \text{ mg mL}^{-1}$, corresponding to an approximately 4.32-fold increase (Welch's t-test, $p < 0.001$). Succinic-acid-based multicomponent systems have previously shown system-dependent improvements in solubility or dissolution (Erizal et al. 2020b; Majeed et al. 2017); However, because the functional comparison did not include the PRX-SUC physical mixture or a spherically processed PRX control, the individual contributions of SUC, solid-state transformation, and particle-level modification to the observed solubility difference cannot be quantitatively separated.

Dissolution testing using a paddle-over-stationary-disc configuration showed higher PRX release from Sph-PRX-SUC than from untreated PRX (Figure 7). At 5 min, cumulative dissolved PRX was $1.15 \pm$

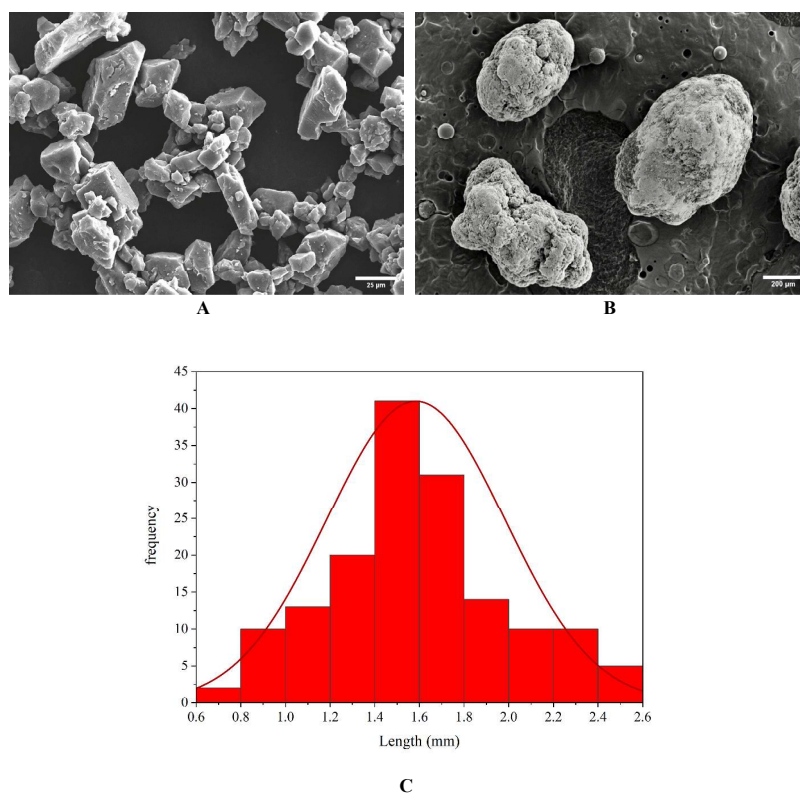
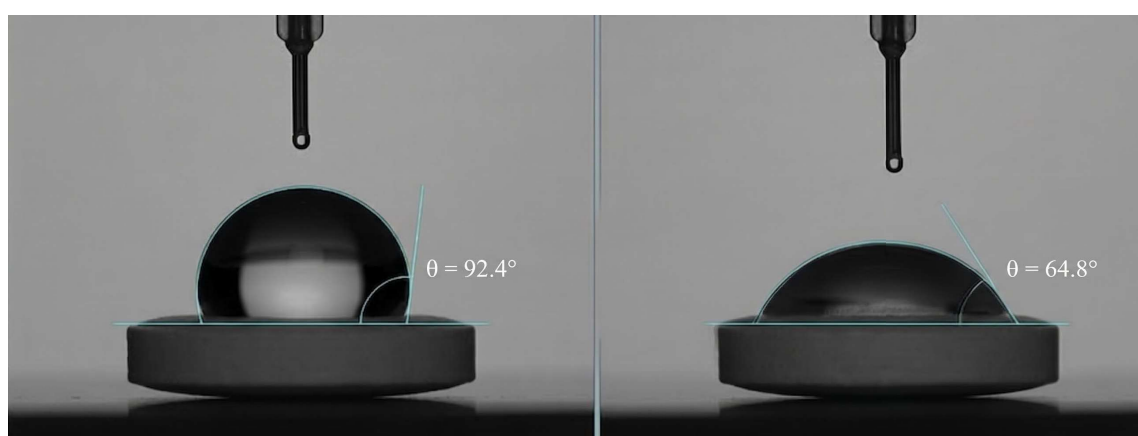


FIGURE 5. Morphology and particle-size distribution of PRX and Sph-PRX-SUC: (A) SEM micrograph of PRX, (B) SEM micrograph of Sph-PRX-SUC, and (C) particle-size distribution of Sph-PRX-SUC obtained by image analysis

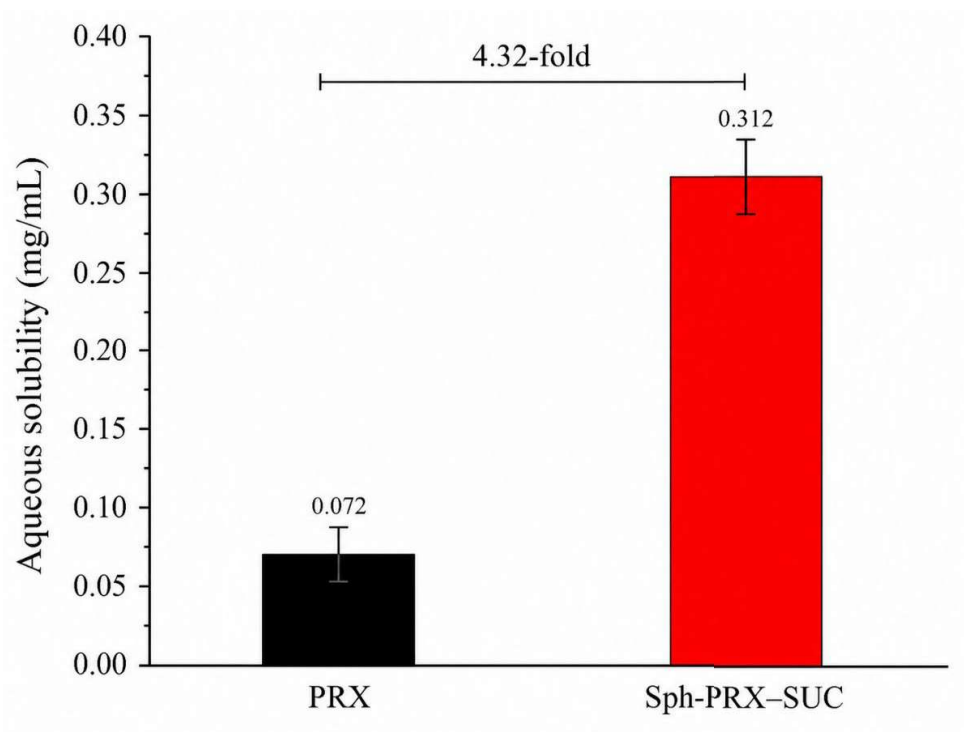
TABLE 1. Micromeritic properties of PRX and Sph-PRX-SUC

Parameter	PRX	Sph-PRX-SUC
Angle of repose (°)	42.56 ± 1.75	32.86 ± 1.06
Bulk density (g/mL)	0.310 ± 0.005	0.390 ± 0.009
Tapped density (g/mL)	0.652 ± 0.011	0.482 ± 0.019
Hausner ratio	2.11 ± 0.04	1.23 ± 0.03
Carr's compressibility index (%)	52.52 ± 0.81	18.98 ± 1.78
Flow rate (g/s)	0.162 ± 0.005	1.62 ± 0.17

Values are presented as mean ± SD



A



B

FIGURE 6. Wettability and apparent aqueous PRX solubility of PRX and Sph-PRX-SUC: (A) water contact angle and (B) apparent aqueous PRX solubility determined directly by UV-Vis spectrophotometry using a PRX calibration curve. Data are presented as mean ± SD (n = 3)

0.08 mg cm⁻² for Sph-PRX-SUC compared with 0.21 ± 0.02 mg cm⁻² for PRX, while at 60 min the corresponding values were 12.85 ± 0.45 and 2.75 ± 0.10 mg cm⁻², respectively. The dissolution profiles were linear over 5–60 min for all individual replicates, with *r*² values ranging from 0.9955 to 0.9981 for PRX and from 0.9959 to 0.9988 for Sph-PRX-SUC. The corresponding IDRs were 0.04634 ± 0.00063 and 0.21252 ± 0.00462 mg cm⁻² min⁻¹, respectively, representing an approximately 4.59-fold higher IDR for Sph-PRX-SUC (Welch's *t*-test, *p* < 0.001).

Both compact types remained macroscopically intact throughout the 60-min test, with no cracking, fragmentation, or edge loss; only a gradual reduction in thickness was observed. Because each compact was retained in the holder with only one 8 mm circular face exposed, this thickness reduction represented recession of the exposed surface without increasing the nominal exposed area of 0.50 cm². Sink conditions were also maintained. Using the measured aqueous PRX solubility of 0.072 mg mL⁻¹ as a conservative reference, 900 mL of medium provided a saturation capacity of approximately 64.8 mg, whereas the maximum amount dissolved from Sph-PRX-SUC was approximately 6.43 mg, corresponding to only ~9.9% of this capacity.

The higher dissolution of Sph-PRX-SUC occurred alongside its lower contact angle, higher apparent

aqueous PRX solubility, altered solid-state characteristics, and different particle morphology. These observations demonstrate the overall dissolution performance of the processed Sph-PRX-SUC system; however, the present controls do not permit the individual contributions of coformer incorporation, solid-state transformation, wettability, and particle-level modification to be resolved (Ammanage et al. 2020).

TABLETABILITY AND TENSILE STRENGTH

Tensile strength increased with compression pressure for both samples, with Sph-PRX-SUC consistently producing stronger compacts than untreated PRX (Figure 8). At 50, 100, 150, and 200 MPa, tensile strengths were 0.43 ± 0.05, 0.66 ± 0.08, 0.84 ± 0.12, and 0.96 ± 0.16 MPa for PRX and 1.18 ± 0.05, 2.14 ± 0.07, 2.96 ± 0.17, and 3.54 ± 0.18 MPa for Sph-PRX-SUC, respectively. Sph-PRX-SUC showed significantly higher tensile strength at all compression pressures (Holm-adjusted Welch's *t*-tests, *p* < 0.001). The higher tensile strength was accompanied by differences in particle morphology, particle-size distribution, and micromeritic behaviour. However, because compact porosity, true density, elastic recovery, and deformation behaviour were not independently characterised, the individual mechanisms underlying the altered compaction response cannot be resolved.

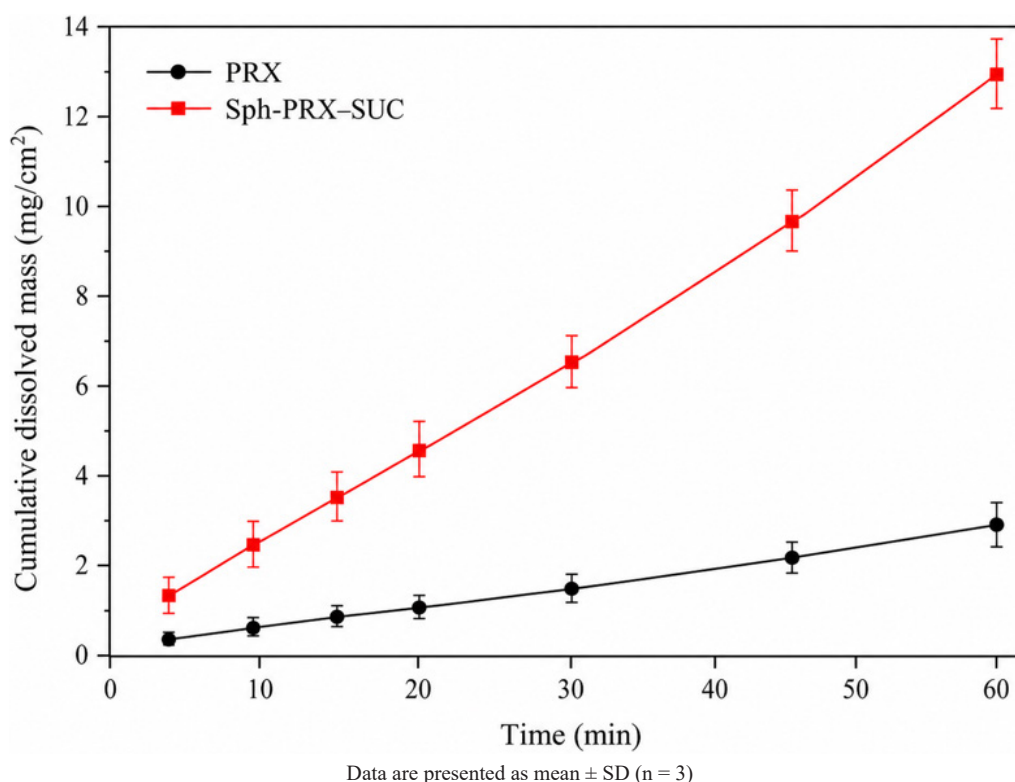


FIGURE 7. Intrinsic dissolution profiles of PRX and Sph-PRX-SUC obtained using a paddle-over-stationary-disc configuration with USP Apparatus 2. Cumulative dissolved PRX was normalised to the nominal exposed compact area of 0.50 cm²

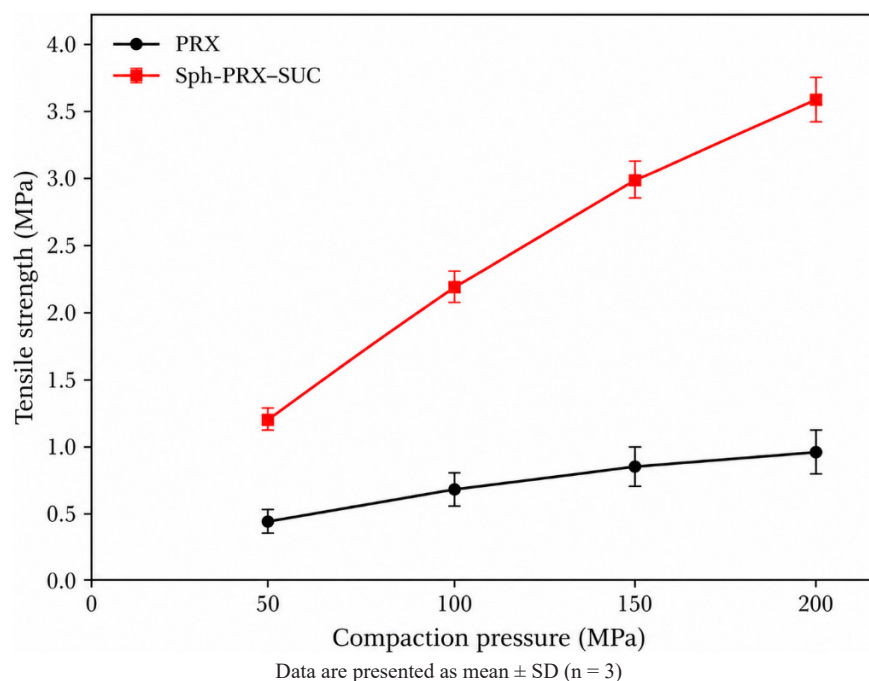


FIGURE 8. Tableability profiles of PRX and Sph-PRX-SUC. Tablet tensile strength was plotted as a function of compaction pressure

CONCLUSION

Spherical crystallisation of piroxicam with succinic acid produced Sph-PRX-SUC with distinct solid-state and particle-level characteristics. PXRD comparison with PRX polymorphs and reported PRX-SUC phases supported the formation of a distinct PRX-SUC multicomponent crystalline phase, while complementary spectroscopic and thermal analyses indicated altered molecular and thermal behaviour. Sph-PRX-SUC formed rounded millimetre-scale agglomerates with more favourable micromeritic properties than untreated PRX. It also exhibited lower contact angle, higher apparent aqueous PRX solubility, higher IDR, and greater tensile strength. At 200 MPa, tensile strength increased from 0.96 ± 0.16 to 3.54 ± 0.18 MPa, demonstrating improved neat-powder tableability under the tested conditions. Overall, the processed Sph-PRX-SUC system combined distinct solid-state and particle characteristics with improved dissolution-related and compaction performance. However, because the functional comparisons did not independently control coformer, solid-state, and particle-level effects, their individual contributions cannot be resolved from the present study.

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