

Evaporative coupled with antisolvent crystallization for additive manufacturing of personalized solid dosage forms

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ABSTRACT

Flexible solid dosage manufacturing platforms that enable customizing doses for personalized medicine, are recognized as the future standard in pharmaceutical therapy. This study uses a solution-based additive manufacturing approach for the solid dosage formulation of individualized doses, precisely controlled in increments as little as 0.2 mg. The drug substance warfarin sodium isopropanol (WS-IPA) has relevant personalized formulation needs and was used as the highly potent model compound. A solution (drug substance, solvent, antisolvent, polymer) is dispensed into a capsule carrier (pullulan) based on a model-informed precision dosing algorithm to manufacture crystalline solid dispersion (CrySoD). Upon a controlled evaporative antisolvent-solvent crystallization (heptane/IPA), WS-IPA crystallizes inside the polymer matrix (polyethylene glycol, PEG). By controlling the critical process parameters (temperature, drug substance – PEG concentration, antisolvent composition) of the coupled crystallization and formulation process, the commercial crystalline solid form of WS-IPA can be obtained. The CrySoD capsules (commercial and individualized doses) met key performance metrics (e.g., dissolution profile) of commercially formulated WS-IPA tablets (Coumadin®) following United States Pharmacopeia (USP) protocols. The workflow and insights provide a generalizable proof-of-concept for a model-informed solid dosage formulation platform enabled by process intensification. This study might be used as a rationale for further investigations, including other personalized medicine relevant drug substances, regulatory science, and technoeconomic analysis.

1. Introduction

A recent study (Mbodji et al., 2025) reported a generalizable proof-of-concept of a solution-based additive manufacturing platform for solid dosage formulation inside a capsule carrier to eliminate the need for cumbersome handling of solids while also reducing the number of unit

operations via process intensification. (Stelzer et al., 2020) In addition, the solution-based approach addresses the limitations often associated with suspension-based strategies such as clogging (Leung, 2022; Patel et al., 2021; Garba-Mohammed et al., 2025) and non-isokinetic feed (Stelzer et al., 2020; Myerson et al., 2019), which lead to dosing inaccuracies and drug content non-uniformity in the formulated product.

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(Kulshreshtha et al., 2009; Goel, 2024) In the reported solution-based approach (Mbodji et al., 2025) the solid dosage form is generated inside a polymeric capsule carrier by utilizing crystallization as a tool for product design. (Stelzer and Ulrich, 2010; Ulrich et al., 2011) Specifically, by controlling the evaporative crystallization process (Hellstén et al., 2013) the active pharmaceutical ingredient (API) modafinil was crystallized within a polyethylene glycol (PEG) matrix to generate a crystalline solid dispersion (CrySoD). (Chiou and Riegelman, 1971; *To prevent confusion, in this work the abbreviation CrySoD (Crystalline) and ASoD (Amorphous) are used for Solid Dispersions. The abbreviation CSD is commonly used in the field of Pharmaceutical Sciences and Industrial Crystallization for two different meanings.) This coupled crystallization and formulation process for *in situ* CrySoD generation also ensured the critical control of the API's commercial polymorphic form to meet regulatory requirements. (Mbodji et al., 2025) The CrySoDs quality attributes were similar to those of the commercial tablets (Provigil®) following US Pharmacopeia (USP) methods, (Mbodji et al., 2025) while demonstrating a flexible (additive) formulation approach for solid dosage forms needed for, e.g., personalized/individualized dosing (Martínez-Jiménez et al., 2025).

Personalized medicine is increasingly recognized as the future standard of care in pharmaceutical therapy, necessitating a fundamental shift in formulation technologies that enable customizing dose, dosage form, administration time, drug release kinetics, and manufacturing platforms to meet individual patient needs. (Martínez-Jiménez et al., 2025; Lewin et al., 2016; Jamróz et al., 2018; Rantanen and Khinast, 2015; Rajjada et al., 2021) However, today's conventional solid dosage drug product manufacturing (large-scale and fixed-dose), most commonly tablets and capsules, do not adequately address the personalized needs of many patients. (Martínez-Jiménez et al., 2025; Lewin et al., 2016; Azad et al., 2018; Aunon-Chancellor et al., 2020) To date required dose adjustments are made via, e.g., splitting of tablets or administering combinations of commercial tablets with different dose strengths as well as in specialized compounding pharmacies. (Elliott et al., 2014; Shah et al., 2010; Kurćubić et al., 2021) All these approaches have documented challenges in terms of, e.g., drug content uniformity and maintaining current good manufacturing practice. (Martínez-Jiménez et al., 2025; Chaudhri et al., 2019) In addition, personalized medicine means moving closer to a more precise and predictable drug product delivery that permits customizing the dose strength for each individual utilizing, e.g., model-informed precision dosing. (Martínez-Jiménez et al., 2025; Reyes-González et al., 2020) The latter represents a forward-looking personalized medicine approach that addresses current challenges of the one-size-fits all strategy, including cost reduction and drug delivery optimization for individuals with rare or complex conditions or for certain sub-groups. (Martínez-Jiménez et al., 2025; Reyes-González et al., 2020) Specifically, model-informed precision dosing uses pharmacokinetic and pharmacodynamic models in combination with specific data (e.g., genetics, demographics, and clinical factors) to optimize and individualize drug therapy. (Martínez-Jiménez et al., 2025; Reyes-González et al., 2020) Consequently, regulatory agencies, e.g., the Food & Drug Administration (FDA) (Hamburg, 2013) and European Medicines Agency (EMA) are increasingly emphasizing the need for personalized dose formulation approaches. (Martínez-Jiménez et al., 2025) However, the translation into practical approaches is still sparse, emphasizing the need for innovative technologies to deliver the full potential of personalized medicine. (Martínez-Jiménez et al., 2025; Dzau et al., 2015; Dzau et al., 2016; Marchiano et al., 2021; Gadelha et al., 2022).

Motivated by these unmet needs, the present work builds on the recently published solution-based additive manufacturing approach (Mbodji et al., 2025) to report a proof-of-concept for the generation of solid dosage forms with individualized doses (extracted from literature) utilizing a model-informed precision dosing algorithm. (Reyes-González et al., 2020) Warfarin sodium isopropanol (WS-IPA, hemisolvate, BCS Class I (Forbes et al., 2025), a racemic compound, was chosen as a FDA

approved highly potent (Karlsson et al., 2007) model drug, (Food and Drugs and Administration, 2012) relevant to personalized medicine. (Martínez-Jiménez et al., 2025) WS-IPA is used for the preventive treatment of thrombosis and "heart attacks" (myocardial infarction). (Food and Drugs and Administration, 2012) Despite the development of new-generation anticoagulants, (Brem et al., 2013) WS-IPA is listed as an essential medicines by the World Health Organization (WHO). (World Health Organization, 2021) WS-IPA is characterized by a narrow therapeutic index (Food and Drugs and Administration, 2015) requiring precise and individualized dosing to avoid significant adverse effects that frequently lead to hospitalizations. (Nguyenpho et al., 2015; Ansell et al., 2008) Further details about the personalization needs for WS-IPA are provided in Section S1. WS-IPA is marketed as solid dosage form (tablets) under the trade name Coumadin® with as many as nine different dosage strengths (Food and Drugs and Administration, 2012) to enable individualized dosing needs. (Martínez-Jiménez et al., 2025) The availability of as many as nine different dosage strengths for WS-IPA is highly exceptional. For almost all other drugs reported relevant to personalized medicine, conventional mass production provides a one-size-fits-all preestablished amount of drug substance in only one or two fixed solid dosages. (Martínez-Jiménez et al., 2025) Recent studies reported the development of oro-dispersible films containing WS-IPA for personalization. However, these films presents content-uniformity challenges arising from film cutting (Niese and Quodbach, 2019; Forbes et al., 2024) and the known moisture sensitivity (Jacob et al., 2023) of WS-IPA renders film formulations as incompatible. (Gao and Maurin, 2001) Moreover, while solid form control (e.g., crystalline, amorphous, polymorph, solvate) in conventional formulation processes (e.g., tableting) (López-Mejías et al., 2012; Nadgorny et al., 2016; Alhijaj et al., 2019; Shahbazi and Jäger, 2021) is widely reported, a similar level of understanding for personalized and additively manufactured drug products has yet to be developed. (Mbodji et al., 2025) This is remarkable considering the regulatory agencies demand proof of solid form control. (Food and Drugs and Administration, 2026; Yu et al., 2014; Mohammed et al., 2015).

To ensure robust manufacturing of WS-IPA CrySoD, the critical process parameters (CPPs) of the crystallization process (solvent, temperature, concentration and antisolvent ratio) as well as key performance metrics of the solid dosage form were identified and evaluated. For the characterization, a wide array of techniques was employed, including powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetry analysis (TGA), ultraviolet-visible (UV-vis) spectroscopy, and gas chromatography (GC). In accordance with USP methods for drug content, content uniformity, and dissolution studies, the performance of the WS-IPA CrySoD was compared with commercial WS-IPA (Coumadin®) tablets. (Food and Drugs and Administration, 2012).

Ultimately, the present study belongs to a series of efforts towards an end-to-end pharmaceutical manufacturing platform of WS-IPA for point-of-use application, starting with the API synthesis, (Silva-brenes et al., 2024) its purification, and the individualized final drug product formulation. The latter being reported in this work.

2. Materials and methods

2.1. Materials

Heptane, isopropanol (IPA), phosphate buffered saline (PBS) tablets, phosphorus pentoxide (P₂O₅), polyethylene glycol (PEG; average molecular weight 10,000 g/mol), pullulan capsules (size #0), warfarin sodium isopropanol (WS-IPA) and WS-IPA tablets (Coumadin®) (Food and Drugs and Administration, 2012) were purchased from commercial sources. Details of the suppliers, CAS registry numbers, and purity as provided by the chemical suppliers are described in Table S1. Ultra-high purified water was obtained from a water purification system (Gemini, Aries Filter). All materials were used as received without additional

purification.

2.2. Methods

Determination of Quaternary Phase Diagrams for CrySoD Design Space. A method previously reported was modified. (Mbodji et al., 2025) Briefly, physical mixtures between (20 – 80 wt%) of PEG in WS-IPA were prepared by gently grinding the mixtures for ≤ 3 min using a mortar and pestle at ambient conditions in the absence of solvents. (Mbodji et al., 2025; Sanabria Ortiz et al., 2020) Saturated solutions of each physical mixture were generated by adding excess of solids into 8 mL vials (VWR) with 2 mL of IPA – heptane (17 v/v%). (George De La Rosa et al., 2019) Employing the Crystalline platform the capped vials were submitted to different isothermal temperatures ranging from 20 to 40 °C under vigorous stirring at 700 rpm using standard 10 mm magnetic stir bars. After ≥ 72 h, the agitation was stopped for ≥ 1 h to allow the remaining solids to settle before withdrawing ~ 1 mL of supernatants, which were immediately filtered through 0.22 μ m PTFE syringe filters (VWR, 13 mm diameter) into new 2 mL vials (VWR) at ambient temperature. Aliquots of 0.1 mL were swiftly transferred to 25 mL volumetric flasks (PYREX) and diluted with the binary IPA – heptane (17 v/v%) solvent-antisolvent system. The concentrations of WS-IPA and PEG in the solutions were quantified using an offline Cary 100 Series UV-Vis spectrometer (Agilent Technologies), detailed in section 2.3 below. Calibrations curves (Fig. S3) were used to calculate the concentrations of WS-IPA and PEG. Preliminary experiments were conducted to determine the optimal equilibration time of 72 h for the system studied employing the isothermal method (section S7). In this study, ambient conditions are defined as 23 ± 2 °C and $65 \pm 5\%$ RH while vacuum desiccator (-0.05 MPa) conditions with P_2O_5 are defined as 23 ± 2 °C and $25 \pm 3\%$ RH.

Crystalline Solid Dispersion (CrySoD) Preparation. To validate the thermodynamic design space, CrySoDs of WS-IPA and PEG (MW 10,000) were prepared employing a modified solvent evaporation method adopted from prior publication, (Mbodji et al., 2025) coupled with antisolvent addition. As a note, PEG is an FDA approved polymer excipient, (Milton Harris and Chess, 2003) widely used in CrySoD preparations. (Mbodji et al., 2025; Sanabria Ortiz et al., 2020; Eloy and Marchetti, 2014) PEG is also considered as a green solvent (Hoffmann, 2022) and co-solvent (Mbodji et al., 2025; Rath et al., 2018; Thimmasetty et al., 2020) to enhance drug solubilities.

For the CrySoD preparation 100 mg of WS-IPA and PEG were individually weighed into 8 mL glass vials (VWR) between 20 – 80 wt% PEG, respectively, utilizing an analytical balance (detailed above). Thereafter, 6 mL of IPA was added to the vials and immediately capped and placed in the Crystalline multiple reactor system (Technobis Crystallization System) kept at 60 °C under vigorous stirring (standard 1 cm magnetic bar at 700 rpm) until complete dissolution was achieved utilizing the transmissivity signal. These solutions were then swiftly filtered at ambient temperature through a 0.22 μ m polytetrafluoroethylene (PTFE) syringe filter (VWR, 25 mm diameter) into new 20 mL glass vials (VWR). Based on previously reported WS-IPA solubility data, (George De La Rosa et al., 2019) 1.2 mL heptane (17 v/v%, antisolvent with respect to the prepared solutions) was added manually to each vial at ambient temperature using a micropipette (Eppendorf). The vials were stored uncapped in a vacuum desiccator with P_2O_5 at ambient temperature and controlled RH (defined above) until solvent-antisolvent were visually evaporated within 7 to 10 days independent of the dispensed volume. The solids recovered were carefully removed and quickly ground using a mortar and pestle for ≤ 2 min at ambient conditions in the absence of solvent before conducting immediately solid-state characterization by PXRD. Remaining sample amounts were stored in a vacuum desiccator. Preliminary experiments confirmed by PXRD that the increased energy input by grinding does not induce a solid form change (Fig. S2). (Brittain, 2009).

Customized Setup for Capsule Filling. A customized capsule filling

setup (Fig. 1) previously reported, (Mbodji et al., 2025) was used for the additive manufacturing. As the present study builds on this prior work, only a brief overview is provided for context. The system consisted of a temperature-controlled syringe pump fitted with a 20 mL Luer-lock syringe (BD). An aluminum platform (McMaster Carr, IL), customized in-house, served as the capsule holder at ambient conditions during the capsule filling process.

Additive Manufacturing of WS-IPA Capsules. An in-house fabricated customized capsule filling setup (Mbodji et al., 2025) (Fig. 1) was employed to produce CrySoDs of WS-IPA filled in pullulan capsules, commonly employed in the pharmaceutical industry. (Cheng et al., 2011; Farris et al., 2014) Briefly, a saturated solution of WS-IPA ($C_{WS-IPA} = 14$ mg/mL_{solvent}) containing PEG (20 wt% relative to the WS-IPA – PEG physical mixture) in the binary IPA – heptane (17 v/v%) solvent-antisolvent system, temperature-controlled at 55 °C, was manually dispensed on demand at 0.2 mL/min (not claimed to be optimized) into the capsules. The commercial (Food and Drugs Administration, 2012) and individualized (Reyes-González et al., 2020) doses per unit (capsule, Table S2) were achieved by dispensing between 0.072 – 0.715 mL of the WS-IPA solution (Table S4). Capsules were kept in a vacuum desiccator under P_2O_5 at ambient temperature and controlled relative humidity defined above for solvent-antisolvent (IPA-heptane) evaporation. Typically, the solution solidified visually within 2 to 3 days, yielding to the formation of WS-IPA CrySoD. Based on the CrySoD preparation (detailed above), it was decided to keep the capsules for ≥ 7 days to ensure complete solvent-antisolvent evaporation. Optimizing the evaporation process to shorten the time by e.g., increasing temperature or reducing the pressure is beyond the scope of this work. (Hellstén et al., 2013) Representative capsules from each target dose (assumed free of solvent-antisolvent) were characterized by PXRD, DSC, and TGA to confirm solid form prior to drug content, content uniformity and dissolution studies. In this study, the USP monograph for WS-IPA tablets were adapted because a monograph for WS-IPA capsules has not been documented. (United States Pharmacopeia, 2024) In addition, gas chromatography (GC) analysis was conducted for determination of residual antisolvent (heptane).

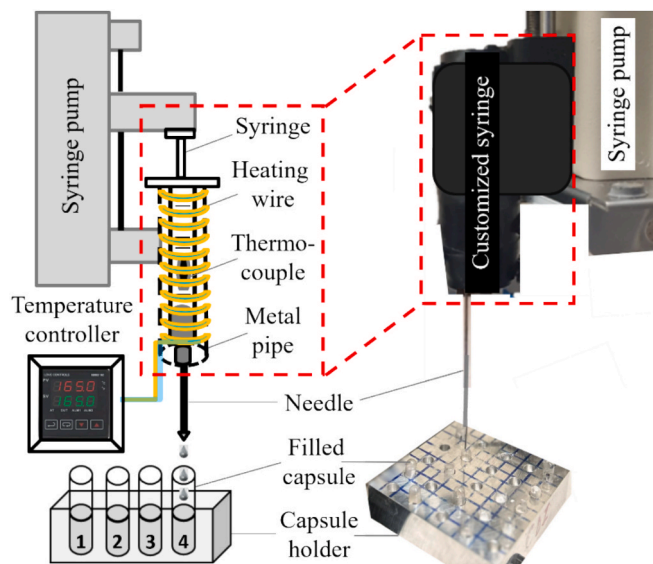


Fig. 1. Experimental setup for solution-based additive manufacturing of WS-IPA CrySoD in commercial capsules; (left) schematic representation and (right) picture. Details of the customized syringe in the schematic representation are indicated by the red frame. Adapted with permission from Mbodji et al. (Mbodji et al., 2025) Copyright 2025 Elsevier.

2.3. Characterization

Sample Preparation for Characterization. Depending on the analytical methods employed in this study, representative samples were prepared accordingly. Due to small quantities of solids per capsule (≤ 12 mg), the CrySoD capsules were gently ground within the capsule shell using a small spatula under ambient conditions for ≤ 2 min. Appropriate amounts of the powdered samples were removed from the capsule shell and immediately characterized by PXRD, DSC, and TGA to minimize exposure to ambient moisture. (Gao and Maurin, 2001; Sheth et al., 2004) For GC, drug content, content uniformity, and dissolution studies, the CrySoD capsules were analyzed as manufacturing without removing the capsule shell and grinding.

UV – Vis Spectroscopy. A Cary 100 Series UV–Vis spectrometer (Agilent Technologies) was used to determine the calibration curves for WS-IPA and PEG in IPA – heptane (17 v/v%) (Fig. S3) as well as IPA and phosphate buffered saline (PBS; pH 6.8) (Fig. S8). Each calibration curve was obtained using five standard solutions of each compound, prepared from stock solutions (1 mg/mL) in five 10 mL volumetric flasks (PYREX) by the consecutive dilution method. (Schmid, 2001; Famili et al., 2011) The calibration curves (Figs. S3b and 3d) were utilized to compute the concentrations of WS-IPA and PEG for the quaternary phase diagram, drug content, content uniformity, and dissolution studies. All experiments were performed at controlled temperature of 20 °C. For data collection and analysis, the UV Cary Scan software (version, 200.470) was employed. The absorption spectra of WS-IPA and PEG were recorded between 200 – 800 nm with λ_{max} for WS-IPA and PEG measured at 307 and 514 nm respectively (Figs. S3a and S3c). It should be noted that the detection of PEG in solution by UV–Vis spectroscopy requires the use of the Dragendorff reagent (Mbodji et al., 2025; Jia and Tian, 2009; Fejfer et al., 2021) and does not interfere with the WS-IPA absorption (Fig. S3).

Powder X-ray diffraction (PXRD). A Rigaku XtaLAB SuperNova single microfocus Cu K α radiation ($\lambda = 1.5417$ Å, 50 kV, 1 mA) source equipped with a HyPix3000 X-ray detector in transmission mode was employed to record PXRD diffractograms at ambient conditions. Briefly, the powdered samples were affixed in MiTeGen microloops using a small amount of paratone oil. The diffractograms were collected using the fast phi scan mode with an exposure time of 300 s over an angular 2-Theta (2θ) ranging from 5 to 35° with a step size of 0.01°. Rigaku CrysAlisPro software (v. 1.171.3920a.) was used to record and analyze the data.

Differential Scanning Calorimetry (DSC). A DSC Q2000 from TA Instruments Inc., equipped with an autosampler and RCS40 single-stage refrigeration system, was used to record DSC thermograms. The DSC was calibrated with an indium standard ($T_m = 156.6$ °C and $\Delta H_{\text{fus}} = 28.7$ J/g). A microbalance (XPE26, Mettler Toledo ± 0.002 mg) was used to weigh samples of ~ 5.000 mg in a sealed Tzero aluminum pan without pinhole. The reference was an empty pre-weighed aluminum pan. The samples were equilibrated at 25 °C for 5 min under a N₂ atmosphere (50 mL/min) before heating at 5 °C/min to 230 °C (temperature accuracy of 0.1 °C). The TA Instrument Universal Analysis 2000 software (v. 4.5A) was employed for data collection and analysis of the peak melting temperature (T_m), determined utilizing the linear peak integration function.

Thermogravimetry (TGA) Analysis. A TGA Q500 from TA instruments Inc. was employed to record the TGA thermograms. The TGA was calibrated using a calcium oxalate monohydrate standard. Samples of $\sim 10 \pm 2$ mg were equilibrated at 25 °C for 5 min while heating at 5 °C/min to 230 °C (temperature accuracy of 0.1 °C) under N₂ atmosphere (60 mL/min). The TA Instrument Universal Analysis 2000 Software (v. 4.5A) was used to collect and analyze the data.

Gas Chromatography (GC). Adapted from literature, (Mbodji et al., 2025) the residual antisolvent (heptane) content was determined using a GC system (Model 451) coupled with a headspace sampler (Model 8400). The GC was equipped with a standard split/splitless injector

(split ratio 100:1), a flame ionization detector (FID) set at 200 °C, and a capillary column Rxi-624Sil MS (30 m $\times$ 0.25 mm ID $\times$ 1.4 μ m; Restek Corporation). The analytical method was adopted from literature. (Mbodji et al., 2025; Rahman et al., 2018) Prior to analysis, the headspace syringe was verified for cleanliness by recording a chromatogram of the empty syringe to ensure the absence of solvent or antisolvent residues. A 1 mL aliquot of neat heptane (reference) was transferred into 20 mL headspace vials sealed with screw caps (Agilent), followed by injection of 10 μ L using a headspace syringe (Model 7671; Hamilton). Nitrogen served as the carrier gas at a flow rate of 1 mL/min. For sample analysis, the contents of a single formulated capsule (10 mg dose) were directly transferred into the headspace vial prior to injection. The column was equilibrated at 50 °C for 2 min, then heated at 10 °C/min to 200 °C, with a final hold of 2 min. The total run time per injection was 17.3 min.

Drug Content. The drug content percentage (DC%) of the formulated CrySoD capsules was evaluated following the USP method. (United States Pharmacopeia, 2025) Briefly, 10 formulated capsules of each dose (1 – 10 mg) strength were individually dissolved in 10 mL of neat IPA in a 20 mL sealed scintillation vial maintained at 40 °C on a heating plate (IKA C-MAG HS7) under constant magnetic stirring using a standard stir bar at 700 rpm. Once visually dissolved (≤ 60 min), the solutions were filtered in new 20 mL vials through PTFE syringe filters (detailed above). About 1 mL aliquots were drawn and diluted with neat IPA in 10 mL volumetric flask (PYREX) before being analyzed with UV–Vis spectroscopy (detailed above). Utilizing the linear calibration curve (Fig. S8b, $R^2 = 0.998$) the DC% was computed using eq. (1): (Mbodji et al., 2025; Hill et al., 2009; Rodríguez-Macínéiras et al., 2025)

$$\text{DC\%} = \frac{m_{\text{exp}}}{m_{\text{set}}} 100 \quad (1)$$

where m_{set} and m_{exp} represent the theoretical (set) and measured mass (mg) of WS-IPA, determined employing eqs. (2) and (3), respectively:

$$m_{\text{set}} = c_{\text{set}} V_{\text{dispensed}} \quad (2)$$

$$m_{\text{exp}} = c_{\text{exp}} V_{\text{diluted}} \quad (3)$$

where c_{set} and c_{exp} are set and experimentally measured WS-IPA concentrations in solution (mg/mL), $V_{\text{dispensed}}$ is the dispensed volume (mL) of WS-IPA solution into the capsules during additive manufacturing and V_{diluted} the diluted volume (mL) of analyzed capsule before UV–Vis measurements.

Content Uniformity. Adopted from previous literature, (Mbodji et al., 2025) the content uniformity of 10 formulated capsules was evaluated by determining the concentration in each unit dose via UV–Vis spectroscopy (detailed above). The acceptance value (AV) was calculated using eq. 4. (United States Pharmacopeia, 2025)

$$\text{AV} = |M - \bar{X}| + ks \quad (4)$$

where M represents the target dose of WS-IPA, (United States Pharmacopeia, 2025) $\bar{X}$ the mean of the individual dose expressed as a percentage of the label claim (commercial doses 1 – 10 mg (Food and Drugs and Administration, 2012) and individualized doses, (Reyes-González et al., 2020) Table S2), k the acceptability constant, and s the sample standard deviation ($n = 10$). Since $n = 10$ in this study, $k = 2.4$ according to USP. (United States Pharmacopeia, 2025)

Dissolution Studies. USP monograph for WS-IPA tablets (United States Pharmacopeia, 2024) was adapted to measure the dissolution profiles for generated capsules and commercial WS-IPA tablets (Coumadin®) (Food and Drugs and Administration, 2012) (Table S2) because no guidelines for formulated capsules exist. Adopted from prior literature (Mbodji et al., 2025) the dissolution experiments were conducted in a covered 3 L jacketed beaker (Chemglass, 200 mm inside diameter, 100 mm height) containing 900 mL of PBS (pH 6.8) (United States Pharmacopeia, 2024) and placed on a stirring plate (IKA C-MAG

HS 7 Control model). The solution was temperature-controlled (37 ± 0.5 °C) using a recirculating water bath (Lauda, RA 8). The experiment was conducted under constant agitation at 100 rpm using a cylindrical magnetic stir bar (35 mm length, 8 mm diameter). The temperature was checked when drawing samples using a thermometer immersed in the dilution media. Aliquots of 10 mL were withdrawn every 2 min for the first 10 min and thereafter every 5 min until 1 h. The aliquots were immediately filtered using a $0.22 \mu\text{m}$ hydrophilic PTFE syringe filter (VWR, 25 mm diameter) before being analyzed without dilution using offline UV-Vis spectroscopy (detailed above). The WS-IPA concentration was calculated from the calibration curve of WS-IPA in PBS (pH 6.8, Fig. S8d, $R^2 = 0.997$). The withdrawn volume of the aliquots were replaced immediately with fresh PBS to keep the total volume constant. (United States Pharmacopeia, 2025) The dissolution studies were measured in sextuplet ($n = 6$) for formulated capsules (United States Pharmacopeia, 2025) and in duplicate ($n = 2$) for Coumadin® tablets. (Food and Drugs and Administration, 2012) Adapted from literature, (Mbodji et al., 2025) dissolution profiles between the reference commercial Coumadin® tablets (Food and Drugs and Administration, 2012) and manufactured WS-IPA CrySoD capsules were compared using the relative deviation (RD) and average relative deviation (ARD%) defined in eqs. (5) and (6) as follows:

$$RD = \frac{D_C^i - D_T^i}{D_C^i} \quad (5)$$

$$ARD\% = \frac{100}{N} \sum_{i=1}^N \left| \frac{D_C^i - R_T^i}{R_C^i} \right| \quad (6)$$

where D_C^i and D_T^i are the i th experimental percentage dissolved for the manufactured WS-IPA CrySoD capsules (this study) and Coumadin® tablets, (Food and Drugs and Administration, 2012) respectively, and N represents the total number of experimental values. In this study the experimentally determined percentage dissolved of Coumadin® tablets (Food and Drugs and Administration, 2012) was taken as the reference released rate to calculate RD and ARD%.

3. Results and discussion

3.1. Effect of relative humidity (RH) on WS-IPA crystallinity and its control

Studies have shown that at RH levels $\geq 68\%$, the crystallinity of WS-IPA gradually decreases, leading to its conversion into the amorphous state due to a loss of IPA. (Gao and Maurin, 2001; Sheth et al., 2004; Rugno et al., 2017) Such RH levels can be readily reached under ambient conditions. To ensure that the WS-IPA generated remained in its crystalline form, in this study, samples were prepared and stored under reduced humidity conditions in a desiccator with vacuum and P_2O_5 (23 ± 2 °C and $25 \pm 3\%$ RH). As a side note, it is important to highlight that WS-IPA is a racemic compound hemisolvate, which means that its crystal structure contains 2 molecules of WS and 1 molecule of IPA. The solvent molecule is disordered and trapped inside the crystal lattice and no channel exists for an easy escape of the solvent molecules.

3.2. Effect of solvents on WS-IPA crystallinity

Studies demonstrated that crystallizing WS from neat solvents other than IPA or without being present in solvent mixtures results in gel-like (amorphous) WS. (Gao and Maurin, 2001; George De La Rosa et al., 2019; Hiskey and Melnitchenko, 1965) Since commercially formulated crystalline WS-IPA (racemic compound) is a hemisolvate, (Food and Drugs and Administration, 2012) its crystallization requires employing IPA, (George De La Rosa et al., 2019) entrapped in the crystal lattice at a ratio of WS to IPA of 2:1. (Sheth et al., 2002) It has also been reported

that antisolvent (hexane or heptane) can be used to initiate WS-IPA nucleation, (George De La Rosa et al., 2019) which is otherwise notoriously slow (unpublished data). Therefore, preliminary solution crystallization experiments were conducted to validate the generation of the desired crystalline WS-IPA utilizing heptane as a Class 3 (anti)solvent (United States Pharmacopeia, 2025) at 5 and 20 °C (Fig. S1).

3.3. Thermodynamic design space

It has been demonstrated that ensuring solid form control of the API in additive manufacturing for the generation of solid dispersions (crystalline, amorphous) is paramount as a critical quality attribute (CQA). (Mbodji et al., 2025; Sanabria Ortiz et al., 2020; Figueroa et al., 2024) Therefore, in this study the thermodynamic design space for the solution-based approach (Mbodji et al., 2025) for WS-IPA was determined. It provides an understanding of the CPPs (e.g., WS-IPA and PEG concentrations, solvent-antisolvent choice, temperature) leading to CrySoDs with the desired crystalline form of WS-IPA while ensuring sufficient drug loading (Table S2) per capsule. Upon reviewing the available literature, (George De La Rosa et al., 2019) the solubility of WS-IPA in the presence of PEG at varying composition ratios has not previously been reported for the binary IPA – heptane (17 v/v%) mixtures. Similarly, the solubility of PEG in IPA – heptane mixtures is not yet documented. Therefore, the solubility of PEG (MW = 10,000 g/mol) and WS-IPA at varying composition ratios (20 – 80 wt%) in IPA – heptane (17 v/v%) was measured at 20, 30 and 40 °C prior to the CrySoD generation.

The experimental solubility data at 30 °C are displayed in the quaternary phase diagram (Fig. 2). The values are provided in Table S3. A schematic representation of a quaternary phase diagram and the experimental quaternary phase diagrams at 20 and 40 °C are illustrated in Figs. S5 and S6, respectively. Since the focus of this section is on the identification of the thermodynamic design space yielding to WS-IPA CrySoDs, a detailed discussion of the temperature-dependent solubility of WS-IPA and PEG in IPA – heptane (17 v/v%) is provided in section S8.

The isoplethal section reveals distinct phase domains (Fig. 2). The monophasic region (1) corresponds to an undersaturated solution (white) with respect to WS-IPA and PEG. Two biphasic regions (2) and (3) represent PEG (grey) and crystalline WS-IPA (blue) + saturated solution, respectively. The triphasic region (4), typically the largest domain in this section (Chiarella et al., 2007; Coquerel, 2006; Ricci, 1966) corresponds to the coexistence of WS-IPA and PEG solids with a polysaturated solution (green and orange). While the green sub-domain denotes to conditions under which WS-IPA can be recovered in its crystalline form (≤ 30 wt% PEG), the orange sub-region depicts the amorphous form of WS-IPA (≥ 40 wt% PEG). The exact composition limit was not determined in this study but is assumed to be between 30 and 40 wt% (Table S3 and Fig. S7). Similar observations of the change in the solid-state (crystalline vs amorphous) of organic compounds (e.g., APIs) in the presence of polymers including PEG in various solutions have been reported in the literature. (Eloy and Marchetti, 2014; Douroumis et al., 2007; Zhu et al., 2012; Shahzad et al., 2013).

Based on the determined triphasic sub-domains (green and orange) in Fig. 2, it was hypothesized that upon removal of the solvent-antisolvent (IPA-heptane) by, e.g., evaporation, CrySoDs and ASoDs of WS-IPA can be generated depending on the PEG content in the solution. To test this hypothesis, preliminary experiments to generate solid dispersions by evaporative crystallization were conducted using various WS-IPA – PEG mixtures ranging from 20 to 80 wt% PEG in IPA – heptane (17 v/v%). These experiments (detailed in section 2.2) produced consistently either CrySoDs or ASoDs depending on the PEG threshold between 30 and 40 wt% (Fig. S9). Consequently, it was decided for the further formulation experiments to generate WS-IPA CrySoD with an initial composition of 80 wt% WS-IPA and 20 wt% PEG forming a saturated solution ($c_{\text{WS-IPA}} = 14$ mg/mL) in IPA – heptane (17 v/v%) at

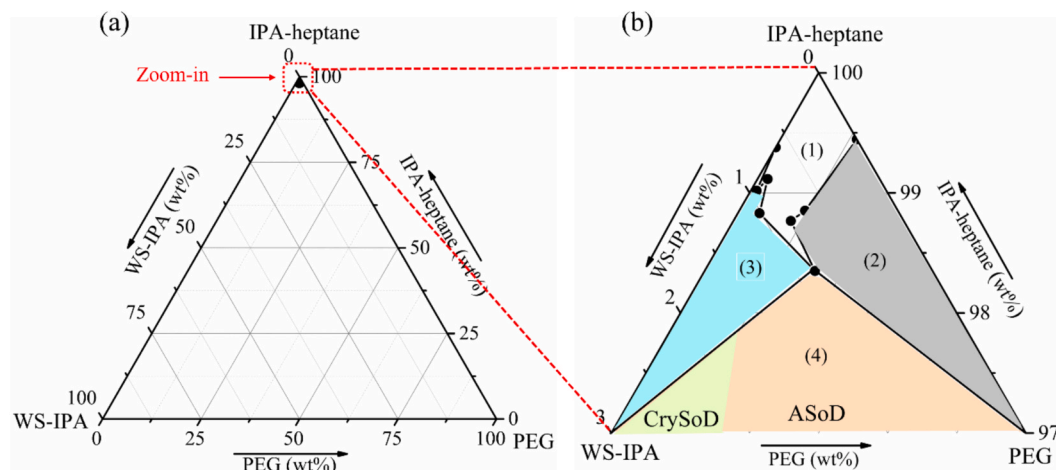


Fig. 2. Isoplethal and isothermal section at 30 °C of the quaternary phase diagram of WS – IPA – PEG – heptane (a) and zoom-in of the (IPA/heptane:17 v/v%) corner (b). Symbols: circles are experimental data and lines are drawn manually to fit the experimental data and to guide the eyes for the limits of phase regions (shaded areas): (1) monophasic (white) represents undersaturated solution, (2) and (3) biphasic representing PEG (grey) and crystalline WS-IPA (blue) + saturated solution, respectively, and (4) triphasic representing WS-IPA + PEG + polysaturated solution. Green and orange areas indicate where WS-IPA can be obtained in its crystalline or amorphous state, respectively, depending on the initial PEG content in the physical mixture. CrySoD and ASoD stand for crystalline and amorphous solid dispersion respectively, (*To prevent confusion, in this work the abbreviation CrySoD (Crystalline) and ASoD (Amorphous) are used for Solid Dispersions. The abbreviation CSD is commonly used in the field of Pharmaceutical Sciences and Industrial Crystallization for two different meanings.) achievable upon evaporation of the solvent-antisolvent, confirmed in preliminary tests (Fig. S9).

55 °C.

3.4. Additive manufacturing of WS-IPA capsules

Capsule Stability. Prior to the solution-based additive manufacturing experiments, the stability of the capsule carrier needed to be assessed. (Mbodji et al., 2025) Previous studies have demonstrated the solubility of commonly used HPMC-based capsules in organic solvents. (Mbodji et al., 2025; Archer, 1992; Williams et al., 2001) Therefore, in this study pullulan (FDA approved) (Singh et al., 2019) was used, which is insoluble in alcohols and other organic solvents, including IPA and heptane. (Farris et al., 2014; Singh et al., 2019) The integrity and stability of representative capsule shells are shown in Fig. 3 (Farris et al., 2014). Other capsule materials, e.g., HPMC, have not been tested within this work.

WS-IPA Solid Form Control. The presence of characteristic WS-IPA diffractogram peaks (Sheth et al., 2004) in the formulated CrySoD

capsules confirms the presence of the commercially desired crystalline form of WS-IPA generated *in situ* within the PEG polymer matrix by a controlled antisolvent (heptane) – evaporative crystallization process, adapted from literature (Mbodji et al., 2025) (Fig. 4). The sharp peaks also suggest the absence of amorphous solids. (Sheth et al., 2004; Holder and Schaak, 2019) In addition, the WS-IPA crystallinity is preserved across all formulated commercial (Food and Drugs Administration, 2012) and individualized (Reyes-González et al., 2020) dose strengths (Fig. 4) as long as the process is operated within the thermodynamic design space for CrySoD (Fig. 2). This conclusion is drawn within the detection limits of the PXRD instrument used in this study. (Newman et al., 2015).

3.5. Analysis of crystalline solid dispersion capsules

Representative capsules (Fig. 3) were tested for drug content quantification, dose content uniformity and dissolution performance, in

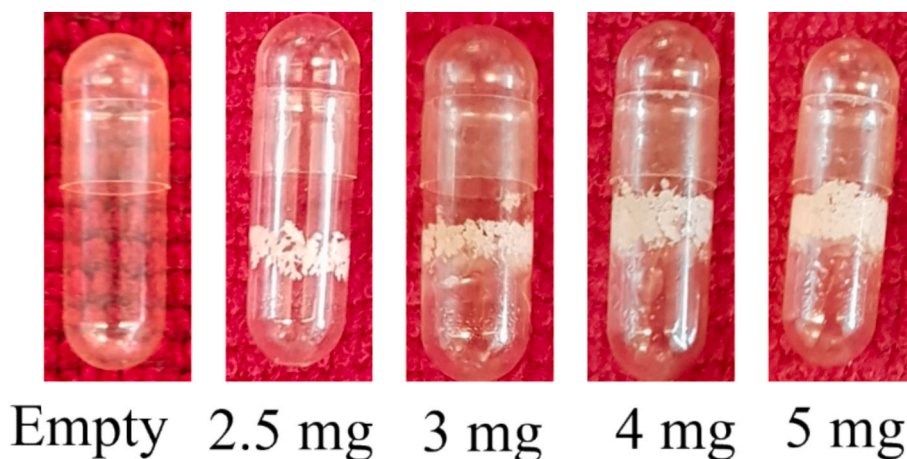


Fig. 3. Photographs of commercial pullulan capsules (size #0): empty (“as received”, control) and manufactured with 2.5; 3; 4; and 5 mg dose strengths of WS-IPA CrySoD obtained after dispensing a WS-IPA solution ($C_{WS-IPA} = 14$ mg/mL in IPA – heptane (17 v/v%) in the presence of 20 wt% PEG. Capsules were kept uncapped inside a vacuum desiccator at conditions detailed above for solvent evaporation ≥ 7 days (not claimed to be optimized). (Hellstén et al., 2013) Once completed, capsules were manually closed for photographs.

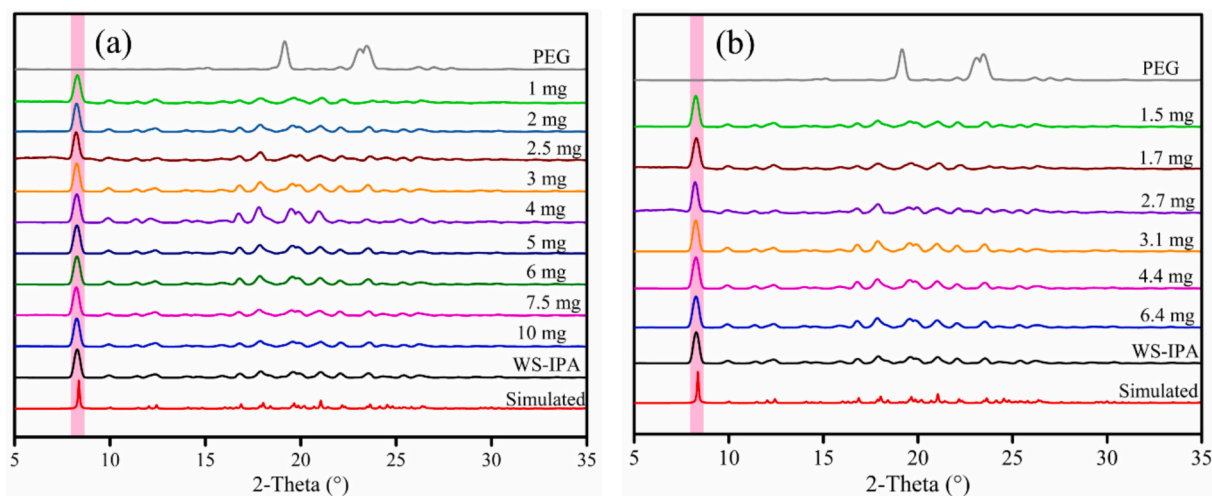


Fig. 4. Normalized powder X-ray diffractograms (PXRD) from bottom to top of simulated WS-IPA (red, CCDC Reference Codes = EFIWIZ and EFIWIZ10) (Sheth et al., 2002) as well as experimental “as received” WS-IPA (black), formulated WS-IPA CrySoD capsules for commercial (a) and individualized (b) dose strengths after physically removing the capsule shell for analysis (various colors), and “as received” PEG (grey). Shaded area indicates the characteristic peak at 8.2° for crystalline WS-IPA. (Shah et al., 2020) Simulated diffractograms were extracted from crystallographic information file obtained from the Cambridge Structural Database (Groom et al., 2016).

accordance with the tests required for commercial WS-IPA tablets (Coumadin®). (Food and Drugs and Administration, 2012; United States Pharmacopeia, 2024) In addition, GC analysis confirmed that the representative capsule formulated for the 10 mg dose in this study was free of residual antisolvent (heptane) within the detection limit of the instrument (10 – 100 ppm; Fig. S11). (Krupčík et al., 2015) Therefore, the heptane content in the formulated capsules must be below the permitted daily exposure (PDE) of < 50 mg (United States Pharmacopeia, 2025).

Drug Content. A critical quality attribute of formulated drug products is the drug content. (Yu et al., 2014) The doses for each commercial and individualized WS-IPA capsule is listed in Table S4. According to USP specifications for WS-IPA tablets, the drug content must fall within $\pm 5\%$ of the label claim. (United States Pharmacopeia, 2024) Across all evaluated dose strengths for commercial and individualized CrySoD capsules, the measured WS-IPA content ($n = 10$ per dose) was close to the target value of 100% (Fig. 5).

The results demonstrated high reproducibility, with an average drug content (DC%) of 99.4 ± 1.2 and 99.3 ± 0.9 for commercial and individualized dose strengths, respectively. Consequently, the CrySoD capsules manufactured in this study are within the USP acceptance range of 95 – 105% for WS-IPA tablets (Coumadin®). (Food and Drugs and Administration, 2012; United States Pharmacopeia, 2024) As a site note, in this study DC% (Fig. 5) was determined using a destructive offline analytical method. (Guan et al., 2015; Qiu et al., 2024) However, it is hypothesized that a load cell could measure the weight of the capsule and non-destructive *in situ* monitoring of the drug concentration could be possible through process analytical technology (PAT), e.g., near infrared or Raman spectroscopy. The monitoring and control through PAT coupled with automation could convert this process into an example of advanced pharmaceutical manufacturing. (Fontalvo Gómez et al., 2019; Románach et al., 2023; Sundarkumar et al., 2022) Although beyond the scope of this work, it highlights the potential for further research.

Content Uniformity. Content uniformity, which evaluates the proximity of individual dose units to the average value, was assessed using eq. 4. (United States Pharmacopeia, 2025) Based on the average DC% detailed above, eq. (4). can be simplified to eq. (7), following USP recommendations. (United States Pharmacopeia, 2025)

$$AV = ks \quad (7)$$

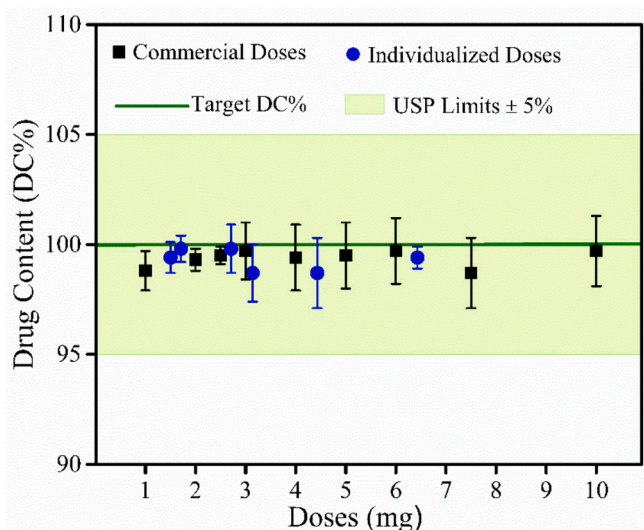


Fig. 5. Drug content percentage (DC%) of commercial Food and Drugs and Administration, 2012 (black solid squares) and individualized (Reyes-González et al., 2020) (blue solid circles) dose units ($n = 10$, Table S2) measured using UV–Vis spectroscopy (Table S4). The green solid line indicates the target (100%) DC% and light green-shaded area represents USP acceptance limits for WS-IPA tablets ($\pm 5\%$, Table S4). (United States Pharmacopeia, 2024).

In eq. (7) $k = 2.4$ (acceptability constant) and s is the calculated sample standard (ranging from 0.9 to 1.2 for 10 formulated capsules at each dose strength). (United States Pharmacopeia, 2025) Consequently, all additively manufactured capsules yielded AV values between 2.9 (commercial doses) and 2.3 (individualized doses), which are at least 5 times smaller compared to the USP limit of $AV \leq 15$ for solid dosage formulations. (United States Pharmacopeia, 2025) Thus, these results demonstrate that the capsule-filling approach reported in this study enables precise dosing of small WS-IPA quantities while generating a solid dosage form.

Dissolution Studies. Dissolution profiles illustrating the percentage of drug release over time for the formulated CrySoD capsules (commercial and individualized dose strengths) are shown in Fig. 6 (United

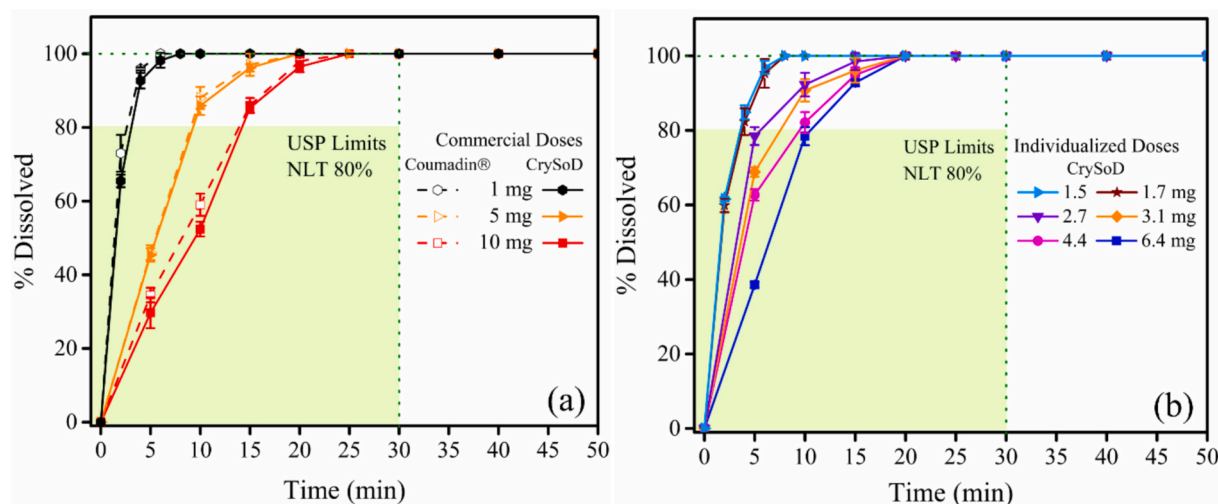


Fig. 6. Dissolution profiles of formulated commercial (a) and individualized (b) WS-IPA CrySoD capsules. For commercial doses (a): opened symbols represent Coumadin® tablets (Food and Drugs and Administration, 2012) served as references and closed symbols WS-IPA CrySoD capsules for 1 (black), 5 (orange), and 10 mg (red) dose strengths as well as for individualized doses (b): closed symbols WS-IPA CrySoD capsules for 1.5 (grey), 1.7 (brown), 2.7 (purple), 3.1 (orange), 4.4 (pink), and 6.4 mg (blue) dose strengths obtained in this study. The green shaded areas indicate the USP acceptance criteria of 80% dissolved WS-IPA amount within 30 min. (United States Pharmacopeia, 2024) The green dotted line illustrates the achieved dissolution amount of 100% of the formulated WS-IPA CrySoD capsules in this study within 30 min. Dissolutions were measured in sextuplet ($n = 6$) for CrySoD capsules and in duplicate ($n = 2$) for Coumadin® tablets. (Food and Drugs and Administration, 2012).

States Pharmacopeia, 2024).

For clarity, only three commercial dose strengths (1, 5 and 10 mg) are included in Fig. 6a, while the remaining strengths are provided in Fig. S12. To evaluate the dissolution performance of the manufactured CrySoD WS-IPA capsules, commercial Coumadin® tablets, (Food and Drugs and Administration, 2012; Kesiosoglou and Wu, 2008) were used as references for comparison. From Fig. 6a WS-IPA CrySoD capsules exhibited dissolution profiles similar to their corresponding commercial counterparts, with a mean $ARD\% = 1.7 \pm 1.3$ calculated from $ARD\%$ for all doses (Fig. S13). The slight delay in the dissolution of the closed CrySoD capsules observed during the first 5 min can be attributed to the time required for the disintegration of the capsule shell, (Stegemann et al., 2014; Radcliffe et al., 2019) which also offers a known pathway for controlled release mechanism. (Mbodji et al., 2025; Mehta, 1993) Following the initial delay the drug release rate increased, reaching completed (100%) dissolution identical to the commercial Coumadin® reference tablets (Food and Drugs and Administration, 2012) within 30 min. Thus, both formulated CrySoD capsules and commercial Coumadin® tablets, (Food and Drugs and Administration, 2012) meet the USP specifications for WS-IPA tablets, requiring $\geq 80\%$ release within 30 min. (United States Pharmacopeia, 2024) In addition, these results indicate that the polymer matrix of the CrySoD does not alter the dissolution profile. (Mbodji et al., 2025; Qiu et al., 2024; Lu et al., 2014; Castro et al., 2013).

For the individualized dose strengths of 1.5, 1.7, 2.7, 3.1, 4.4 and 6.4 mg (Fig. 6b), a direct comparison with commercial products was not possible because corresponding marketed equivalents for these specific dose strengths are not available. A qualitative comparison of these dissolution profiles demonstrates that the individualized doses are within the expected range between 1 and 7.5 mg of the commercial formulated WS-IPA CrySoD capsules. Therefore, the dissolution profiles are only analyzed based on USP criteria. From Fig. 6b the individualized doses depict complete drug release within 20 min, satisfying USP dissolution requirements for WS-IPA tablets (≤ 30 min).

One might argue the impact of the API particle size within the CrySoD on the reported dissolution results (Fig. 6 and S12). (Eloy and Marchetti, 2014) Particle size is considered a CQA for conventional formulations and common method to manipulate the dissolution. (Yu et al., 2014) However measuring the crystal size and distribution of

WS-IPA embedded within the solidified three-dimensional polymer matrix of the presented capsule formulation strategy is not trivial and, thus, beyond the scope of this study. A commonly suggested approach is to destructively dissolve the polymer PEG in a saturated WS-IPA solution to isolate the WS-IPA crystals. However, this strategy assumes that the crystalline API remains insoluble in the selected solvent. Studies have shown that PEG may act as solubility enhancer for APIs, e.g., modafinil. (Mbodji et al., 2025) Thus, as PEG is dissolving in an attempt to isolate WS-IPA crystals, the increasing PEG content will increase the solubility of WS-IPA in the resulting solution, as illustrated in the thermodynamic design space (Fig. 2). Thus, non-destructive method for particle size analysis within the CrySoD WS-IPA capsules would be needed. (Jorgensen et al., 2026) X-ray tomography has been reported as a viable technique (Vijayakumar et al., 2023) suggesting a future research direction of the reported proof-of-concept strategy. (Jorgensen et al., 2026).

4. Conclusion

This study utilizes an antisolvent evaporative crystallization process to formulate CrySoD of WS-IPA as solid dosage forms with solid form control inside a capsule. Moreover, a model-informed precision dosing was used to achieve individualized dosing as a proof-of-concept. The formulation approach consists of dispensing a solution of WS-IPA (API) – IPA (solvent) – heptane (antisolvent) – PEG (polymer) into capsule carriers. Upon evaporation of the solvent and antisolvent a CrySoD is generated inside the capsules. Paramount for the crystallization process design is the determination of the thermodynamic design space within the quaternary system to control the API solid form (crystalline versus amorphous, IPA hemisolvate) within the forming polymer matrix. The CPPs (e.g., WS-IPA and PEG concentrations and their ratios, solvent-antisolvent choice, temperature) alter the solid form of WS-IPA. The WS-IPA CrySoD formulations obtained with commercial and individualized dosage strength similarly met the USP quality criteria for commercial formulations.

The presented workflow and insight provide a generalizable proof-of-concept for a model-informed solid dosage formulation of personalized medicine. Therefore, this study might be used as a rationale for further investigations (e.g., regulatory science, technoeconomic

analysis, optimization of evaporation process).

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CRediT authorship contribution statement

Aliou Mbodji: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrea Arroyo Gomez:** Writing – review & editing, Visualization, Formal analysis. **Gianelle Bigio Silva:** Writing – review & editing, Visualization, Formal analysis. **Cornelis P Vlaar:** Writing – review & editing, Visualization, Formal analysis. **Jorge Duconge:** Writing – review & editing, Visualization, Formal analysis. **Jean-Christophe M Monbaliu:** Writing – review & editing, Visualization, Formal analysis. **Rose K Cersonsky:** Writing – review & editing, Visualization, Formal analysis. **Lian Yu:** Writing – review & editing, Visualization, Formal analysis. **Geoff GZ Zhang:** Writing – review & editing, Visualization, Formal analysis. **Gérard Coquerel:** Writing – review & editing, Visualization, Formal analysis. **Rodolfo J Románach:** Writing – review & editing, Visualization, Formal analysis. **Torsten Stelzer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpharm.2026.127044>. The Supporting Information containing additional details on materials, preparation of crystalline WS-IPA, PXRD of physical mixtures, determination of calibration curves in different solvents, summary of WS-IPA doses formulated in this study, validation of solid-liquid equilibria and solid phase identification, experimental solubility data of WS-IPA – PEG in IPA-heptane and solid phase identification by PXRD at solute solution equilibrium, formulation of CrySoD WS-IPA capsules as well as CrySoD capsules analysis is available free of charge via the journal website.

Data availability

Data will be made available on request.

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