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CONTROLLED API CRYSTALLIZATION DURING ADDITIVE MANUFACTURING OF SOLID DOSAGE FORM FOR FLEXIBLE INTEGRATED PHARMACEUTICAL MANUFACTURING

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Abstract

Conventional manufacturing of solid dosage forms (e.g., tablets, capsules) demands multiple unit operations and handling of solids, known to be more challenging than handling liquids. To circumvent these challenges, this study explored liquid dispensing to manufacture an oral solid dosage form. The presented additive manufacturing process dispenses a solution (drug substance, solvent, polymer) into a carrier (capsule). Upon controlled solvent evaporation, the model active pharmaceutical ingredient, racemic modafinil (MOD), crystallizes inside a polymer matrix (polyethylene glycol) generating a crystalline solid dispersion. The critical process parameters (e.g., temperature, concentration, evaporation rate, choice of solvent) and key performance metrics were evaluated to ensure robust crystalline solid dispersion manufacturing. The coupled crystallization and formulation process delivers the desired polymorph form I of MOD inside a crystalline solid dispersion that matches the quality attributes of commercially formulated MOD tablets (Provigil®) following US Pharmacopeia methods. Moreover, the developed workflow and insights presented provide a generalizable approach applicable to other drug substance – polymer – solvent systems, independent if crystalline or amorphous solid dispersion is needed. Ultimately, this study demonstrates the flexible (additive)

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formulation of solid dosage forms, needed for, e.g., point-of-use manufacturing in remote areas or personalized medicine via a process intensification approach.

1. Introduction

Over the past two decades, innovative processes and techniques have been developed aiming to modernize and streamline the pharmaceutical manufacturing sector. (Mascia et al., 2013, Adamo et al., 2016, Zhang et al., 2018, Rogers et al., 2020, Hausner and Moore, 2022) At the forefront of these efforts are manufacturing platforms that enable flexible, modular, and distributed manufacturing (Adamo et al., 2016, Zhang et al., 2018, Rogers et al., 2020, Lewin et al., 2016, Armstrong et al., 2021, Sundarkumar et al., 2022, Içten et al., 2015). The culmination of such deployable platforms would be their ability to manufacture small quantities of drugs for a smaller number of the population, and potentially even to individuals with specific needs (Lewin et al., 2016, National Academies of Sciences, 2020, Yamamoto et al., 2022). Solid dosage forms (e.g., tablets, capsules), represent about 60 % of all drug formulations due to their favorable oral administration (Awad et al., 2021). Consequently, significant efforts have been undertaken to enable advanced pharmaceutical manufacturing (Romañach et al., 2023) for solid dosage forms across different production scales (Hausner and Moore, 2022, Azad et al., 2018). To date, the conventional formulation of such dosage forms involves multiple powder handling steps, including blending, milling, wet or dry granulation, sieving, and tableting or capsule filling. (Byrn et al., 2015) In recent years, considerable research attention has focused on alternative solid dosage formulation strategies (Mascia et al., 2013, Hirshfield et al., 2014, Clarke and Doughty, 2017, Içten et al., 2016, Içten et al., 2017) aimed at decreasing the number of process and powder handling steps via innovative processing of active pharmaceutical ingredients (APIs) and excipients (Byrn et al., 2015). Documented studies include, formulations based on melt extrusion, (Mascia et al., 2013, Park et al., 2024) film casting, (Panchal et al., 2012, Niese and Quodbach, 2019) electrospinning, (Palo et al., 2017) and especially additive manufacturing has gained popularity (Jamróz et al., 2018, Carou-Senra et al., 2024, Curti et al., 2020, Xu et al., 2022, Patel et al., 2021, Fang et al., 2024, Wang et al., 2022, Martínez-Jiménez et al., 2025). The most promising approaches of additive manufacturing can be categorized into three main concepts: powder solidification, hot-melt extrusion, and liquid solidification. (National Academies of Sciences, 2020, Jamróz et al., 2018) While the first one still requires handling of powders, (Patel et al., 2021) the latter two have been used to fill capsules, utilized as carriers, to generate solid dosage forms by dispensing suspensions containing the crystalline API in a polymer (molten or liquid) or antisolvent (Sundarkumar et al., 2022, Denis et al., 2024, Rodríguez-Maciñeiras et al., 2025, Radcliffe et al., 2019). The final solid dosage formulations are achieved within the capsules by either solidification upon cooling the polymer (Clarke and Doughty, 2017, Denis et al., 2024, Rodríguez-Maciñeiras et al., 2025) or maintaining a liquid suspension (Sundarkumar et al., 2022, Radcliffe et al., 2019, Pardeike et al., 2011). However, these concepts are relatively new and critical technical challenges have not yet been fully resolved. For instance, the approaches reported vastly rely on handling solids within a liquid or melt forming suspensions (heterogeneous systems), known to cause numerous issues, including *(i)* clogging (e.g., nozzle) (Sundarkumar et al., 2022, Carou-Senra et al., 2024, Patel et al., 2021, Leung, 2022), *(ii)* spatial

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heterogeneity in stirred tanks (e.g., feed tank for formulation process) (Stelzer et al., 2020, Myerson et al., 2019, Beckmann, 2013, Paul et al., 2004), and *(iii)* non-isokinetic (non-representative) withdrawal from such stirred tanks at relatively low flow rates (Stelzer et al., 2020) that may yield to suspension metering challenges impacting dosing accuracy and content uniformity (Kulshreshtha et al., 2009, Goel, 2024).

In addition, polymorphism of APIs is a critical quality attribute demanding strict control during drug product manufacturing (Llinàs and Goodman, 2008, Yu et al., 2014). While numerous publications reported polymorphism and solid form control in conventional formulation processes (e.g., tableting, spray drying) (López-Mejías et al., 2012, Nadgorny et al., 2016, Alhijjaj et al., 2019, Shahbazi and Jäger, 2021), a similar level of understanding for additively manufactured drug products has yet to be developed (López Burgos et al., 2023). This is remarkable considering that recent research demonstrated solvent-mediated polymorphic phase transformation in molten polymers (Hernández Espinell et al., 2022) and the impact critical process parameters (CPPs), typical encountered in polymer-based additive manufacturing, (e.g., temperature, pressure, shear stress, residence time) have on the resulting polymorphic form (Hernández Espinell et al., 2018, Reyes Figueroa et al., 2022, Figueroa et al., 2024). This is further pressing as many APIs that are the target of additive manufacturing have demonstrated polymorphism when other processing techniques are used. (Groom et al., 2016) Therefore, regulatory entities will demand strict proof of solid form control (Yu et al., 2014, Mohammed et al., 2015, FDA).

Motivated by recent advances and recognized challenges in additive manufacturing of drug products, this work reports a proof-of-concept study on a solution-based capsule-filling process yielding the API in its commercial polymorphic form, embedded within a polymer matrix forming a crystalline solid dispersion (CrySoD). (Chiou and Riegelman, 1971, The Abbreviation CSD) Unlike suspensions (complex heterogenous liquids), metering of homogenous solutions is less issue-prone and highly accurate. (Kulshreshtha et al., 2009, Goel, 2024) Therefore, in this study the API and polymer are fully dissolved in a solvent allowing precise dispensing into a capsule. The study will demonstrate that this approach yields a CrySoD with polymorphic form control upon solvent evaporation (Sanabria Ortiz et al., 2020).

Racemic modafinil (MOD), polyethylene glycol (PEG), and methanol, were chosen as model drug (Broquaire et al., 2004), polymer matrix (Mascia et al., 2013, Sundarkumar et al., 2022, Içten et al., 2016, Denis et al., 2024, Rodríguez-Maciñeiras et al., 2025, Mura et al., 1999) and, solvent, respectively. MOD is an anti-narcoleptic API prescribed to treat excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work disorder (Teva Pharmaceuticals). Alertec, Madavigil, and Provigil® are commercial trade names of MOD. Among the known seven polymorphic forms (I–VII), two hydrates, and two solvates (Broquaire et al., 2004, Mahieux et al., 2016, Ceausu et al., 2011, Mahieux et al., 2013) of MOD, form I is commercially used (Broquaire et al., 2004). Owing to its cognitive enhancing properties (Kredlow et al., 2019), MOD is the only go pill approved by the US military (U.S. Air Force, 2019) and one of the medications in the International Space Station (ISS) medical kit (Nasa, 2016). Thus, MOD represents a model drug for flexible (additive) solid dosage formulation in remote areas where powder handling is challenging, including, e.g., deep space missions to Mars (NASA 2016, Seoane-Viaño et al., 2022). CPPs and key performance metrics of the introduced formulation platform were identified and evaluated to ensure robust CrySoD manufacturing. A wide array of solid form characterization techniques was employed in this work, including PXRD, Raman

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spectroscopy, DSC, and TGA. In addition, the obtained CrySoDs were compared with a commercial MOD formulation (Provigil®) following US Pharmacopeia (USP) methods for drug content, content uniformity, and dissolution studies (United States Pharmacopeia, United States Pharmacopeia, 2011, United States Pharmacopeia, 2007).

Ultimately, the present study is the continuation of a series of the authors efforts towards the integrated manufacturing of MOD, starting with the API synthesis, (Silva-Brenes et al., 2022) its purification, (Silva-Brenes et al., 2024) and the final drug product formulation (in this work). Collectively, these three studies serve as a proof for an end-to-end pharmaceutical manufacturing platform for point-of-use application with flexible (additive) solid dosage formulation, needed, e.g., in remote areas or for personalized medicine (Adamo et al., 2016, Zhang et al., 2018, Martínez-Jiménez et al., 2025, Seoane-Viaño et al., 2022, Hessel et al., 2022).

2. Materials & methods

2.1. MATERIALS

Racemic modafinil (MOD) form I (≥ 99.5 % purity) was purchased from Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd (Hong Kong). Polyethylene glycol (PEG; ≤ 100 % purity, average molecular weight 10,000 g/mol) was acquired from Alfa Aesar (Ward Hill, MA), Methanol (MeOH; ≥ 99.9 % purity, HPLC grade) from VWR (Radnor, PA), and Hydrochloric acid (HCl; 37 % concentration) from Millipore Sigma (Milwaukee, WI). Hydroxypropyl methylcellulose (HPMC) capsules (size #000) were purchased from LFA Capsule Fillers (Fort Worth, TX). Ultra-high purified water (18.23 MOhm/cm) was obtained from a water purification system (Gemini, Aries Filter). All materials were used "as received" without further purification.

2.2. METHODS

Crystalline Solid Dispersion (CrySoD) Preparation. CrySoDs of MOD form I and PEG were prepared for preliminary analysis using the solvent evaporation method reported in the literature (Sanabria Ortiz et al., 2020). Briefly, physical mixtures of 100 mg between 10 – 80 wt% of MOD form I in PEG were weighed into 20 mL scintillation vials using an analytical balance (MS104S, Mettler Toledo, precision ±0.1 mg). Upon addition of 10 mL MeOH, the mixtures were dissolved at 50 °C under constant magnetic stirring at 700 rpm using a heating plate. Once visually dissolved, the solutions were filtered through a polytetrafluoroethylene (PTFE) syringe filter (25 mm, 0.2 µm pore size, VWR) into new 20 mL scintillation vials covered with perforated parafilm for slow solvent evaporation in a ventilated fume-hood at ambient conditions. In this study, ambient conditions are defined as 23 ± 1 °C and 65 ± 5 %RH. The generated solids were carefully removed and gently ground using a mortar and pestle for 3 min at ambient conditions in the absence of solvent. After a storage in a vacuum desiccator with phosphorus pentoxide (P_2O_5) at ambient temperature for < 72 h, solid – state characterization was conducted. Preliminary PXRD analysis confirmed that no polymorphic phase transformation of MOD form I was induced through the increased energy input by grinding (**Fig. S1**). (Brittain, 2009).

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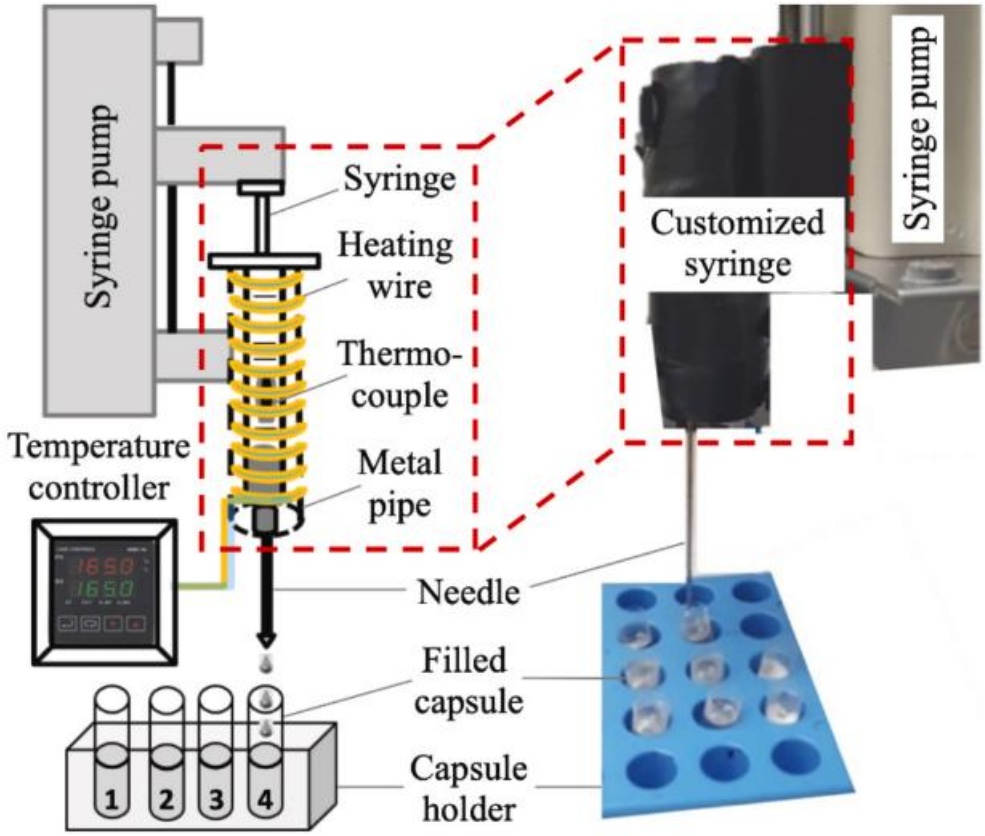
Customized Setup for Capsule Filling. A customized melt depositing system was adapted from the literature (López Burgos et al., 2023) to additively manufacture CrySoDs of MOD in commercially available capsules (size #000, LFA Machines). Briefly, the setup consisted of a syringe pump (Fisher Scientific, MA) and a customized stainless − steel pipe (23.6 mm inner diameter) with a thermocouple (J-type, ± 2.2 °C) affixed and wrapped with a heating wire (610 mm length) and high temperature fiberglass insulation (McMaster Caar, IL) shown in Fig. 1.

Fig. 1. Experimental setup for additive manufacturing of (CrySoDs) in commercial capsules; (left) schematic representation and (right) picture. Red frame details the customized syringe in the schematic representation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



The thermocouple and heating wire were connected to a digital temperature process controller (Dwyer Instrument Inc., 32B-33, ± 0.1 °C). The customized stainless-steel pipe housed a standard 20 mL syringe (BD with Luer Lock) connected with single use needles (18 Gauge, Air – Tite, VA). A standard laboratory 2 mL vial rack (Cole-Parmer) was used as capsule holder platform at ambient temperature. Preliminary experiments demonstrated that maintaining the capsule holder at ambient temperature facilitated achieving the desired CrySoDs with MOD form I in the PEG matrix.

Determination of Temperature – Concentration Design Space for CrySoD. The solubility of PEG in MeOH was determined by employing the isothermal method (Chen et al., 1970, Reus et al., 2015) using the automated multiple reactor Crystalline from Technobis Crystallization System. The isothermal method is commonly employed for solubility determination of polymers, including PEG, in organic solvents. (Wolf et al., 2002, Miller-Chou and Koenig, 2003) In this study, the PEG concentration was determined in triplicate (n = 3) by employing the gravimetric method. (Muller et al., 2009, Guo et al.,

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2014, Trupej et al., 2015) Briefly, saturated solutions of PEG were obtained by adding excess of PEG in MeOH in a glass vial (8 mL, VWR) submitted to different temperatures ranging from 10 to 35 °C. The suspensions were agitated at 700 rpm using magnetic stirring for ≥ 48 h. Thereafter, the agitation was stopped, and the suspensions were allowed to settle for ≥ 1 h before filtering the supernatant using a PTFE syringe filter detailed above. The resulting saturated solutions were transferred quickly in pre-weighed 2 mL glass vials (Fisher Scientific) using an analytical balance (MS104S, ± 0.1 mg). The vials were then placed inside a fume hood under ambient conditions to remove the solvent by evaporation for ≥ 3 days. The vials were weighed daily until a constant mass was obtained for three consecutive measurements.

To determine the MOD solubility in MeOH saturated with PEG (MeOH – PEG), the polythermal method was employed using the automated multiple reactor (Crystal16™, Technobis Crystallization Systems). (Jiménez Cruz et al., 2021, Mbodji et al., 2024, Zorrilla-Veloz et al., 2018, Vázquez Marrero et al., 2019) Briefly, based on the PEG solubility measurements (Table S1, Fig. 2a), the binary MeOH – PEG solutions were prepared for PEG concentrations ranging from 15.9 to 548.2 mg/$mL_{Solvent}$ between 10 to 35 °C, respectively. Thereafter, suspensions composed of MOD and 1 $mL_{Solution}$ of saturated MeOH – PEG solutions were prepared in 2 mL sealed glass vials (Fisher Scientific) at predetermined MOD concentrations. The solute and solvent system were weighed using a microbalance (XPE26, ± 0.002 mg) and an analytical balance (MS104S, ± 0.1 mg) both from Mettler Toledo, respectively. The resulting suspensions were agitated at 700 rpm using rare earth magnetic stir bars while heated at 0.3 °C/min starting from saturated MeOH – PEG temperature (Table S1) to 60 °C. The heating rate of 0.3 °C/min was validated, detailed in section S2.2. (Mbodji et al., 2024, Zorrilla-Veloz et al., 2018, Vázquez Marrero et al., 2019) Assuming that the MOD dissolution kinetics can be neglected in the binary MeOH – PEG solvent system, (Mbodji et al., 2024, Vellema et al., 2011) the light transmission through the suspension can be used to determine the clear point employing the CrystalClear software (version 1.0.1.614). (Jiménez Cruz et al., 2021, Zorrilla-Veloz et al., 2018) The clear point is defined as the temperature at which the solution is free of crystals and thus saturated. (Mbodji et al., 2024) The uncertainty of the measured temperature is within ± 0.1 °C.

Capsule Stability Testing. The stability of the HPMC capsules in the presence of neat solvent (MeOH) or modified binary solvent systems (MeOH – PEG) was evaluated by filling 1 mL of these solvents into the capsules. The experimental tests were conducted in a ventilated-fume hood at ambient conditions to evaporate the solvent. Resulting pictures of capsules in contact with the solvent before and after were recorded to illustrate their deformation/degradation.

Additive Manufacturing of MOD Capsules. CrySoDs of MOD filled in capsules were generated using a customized setup (Fig. 1). Briefly, a saturated solution of MOD (100 mg/$mL_{Solution}$) in the binary MeOH – PEG solvent system (= 548.2 mg/$mL_{Solvent}$), temperature-controlled at 53.5 °C, was dispensed on demand at 0.5 mL/min into the HPMC capsules. The commercial target dose of 100 mg (Teva Pharmaceuticals) per unit (capsule) was achieved by adding 1 mL of the MOD solution. The capsules were then left in a ventilated fume-hood under ambient temperature for MeOH evaporation. Typically, the solution solidified visually in ≤ 30 min, yielding to the formation of MOD CrySoDs. The capsules were frequently weighed until a constant capsule mass was recorded, indicating that MeOH was completely evaporated (Fig. S4). Typically, representative samples of the resulting capsules filled with CrySoD of MOD (assumed free of MeOH) were characterized after ≥ 7 days adapting the USP

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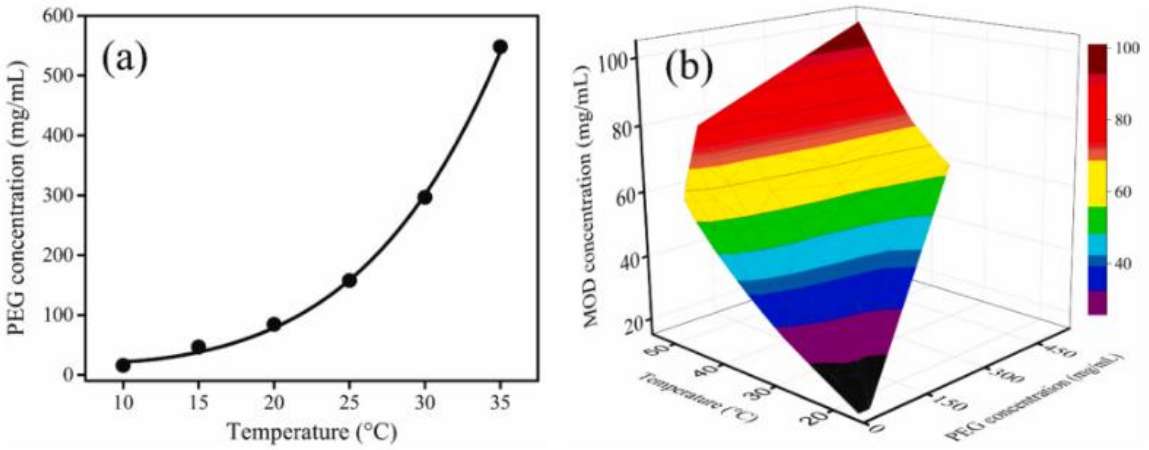
monograph for commercial MOD tablets. (United States Pharmacopeia) In this study, the USP monograph for MOD tablets were adapted because a monograph for MOD capsules has not been documented. (United States Pharmacopeia) The tests include solid form purity, drug content, content uniformity, and dissolution. (Radcliffe et al., 2019, United States Pharmacopeia, 2011) In addition, gas chromatography (GC) analysis was conducted for solvent residual determination.

Fig. 2. Experimental solubility data of (a) PEG in neat MeOH measured using the isothermal method (Mbodji et al., 2024) and (b) Surface plot of MOD in the binary MeOH – PEG solvent system measured employing the polythermal method (Mbodji et al., 2024). If the error bars are not visible, they are covered by the experimental data points (Table S1). The trend line is calculated using the best possible fit (R^2 = 0. 998, polynomial function). Origin (OriginLab Corporation, v. 9.7.0.188) was utilized for the non-linear curve-fitting problems employing the Levenberg-Marquardt algorithm.



2.3. CHARACTERIZATION

Sample Preparation for Characterization. Representative samples were prepared in accordance with the analytical methods employed. For solid form purity (PXRD, Raman spectroscopy, DSC and TGA), the capsule shell was physically removed from the generated CrySoD. The remaining solid was gently ground for 2 min using a mortar and pestle in the absence of solvent and at ambient conditions before conducting the analyses. For drug content, content uniformity, and dissolution studies, the formulated capsules were directly analyzed without removing the capsule shell.

Powder X-ray diffraction (PXRD). PXRD diffractograms were collected at room temperature (23.0 ± 1.0 °C) using a Rigaku XtaLAB SuperNova single microfocus Cu Kα radiation (λ = 1.5417 Å, 50 kV, 1 mA) source equipped with a HyPix3000 X-ray detector in transmission mode. A small amount of paratone oil was employed to affix the powdered samples in MiTeGen microloops. The fast phi scan mode with 300 s of exposure time was employed to collect diffractograms over an angular 2ϑ range of 6 − 50° with a step size of 0.01°. Data were analyzed using Rigaku CrysAlisPro software (v. 1.171.3920a.).

Raman Spectroscopy. Raman spectra were recorded in the range of 350 to 1800 cm^{-1} employing the RXN2 multichannel Raman Analyzer (Kaiser Optical Systems) equipped with a 785 nm laser and a PhAT probe of 6 mm spot size. To avoid the interference of ambient light, the samples were placed on a microscope slide covered with aluminum foil inside a customized 3D – printed polylactic acid black box coupled with the PhAT probe in a 180° backscattering geometry. (Hernández et al., 2022) The

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conditions for the data acquisition were optimized to 60 s exposure time and three accumulations per measurement with cosmic ray filter and intensity correction using the iC Raman software (v. 4.1.917).

Differential Scanning Calorimetry. DSC thermograms were recorded using a DSC Q2000 from TA Instruments Inc., equipped with an autosampler and RCS40 single-stage refrigeration system. The DSC was calibrated with an indium standard (T_m = 156.6 °C and ΔH_{fus} = 28.7 J/g). Hermetically sealed Tzero aluminum pans were used to weigh samples (~4.000 mg) employing a microbalance (XPE26, Mettler Toledo ± 0.002 mg). An empty standard aluminum pan was employed as a reference. Samples were equilibrated at 25 °C for 5 min under a N_2 atmosphere (50 mL/min) before heating at 5 °C/min to 250 °C (temperature accuracy of 0.1 °C). Data collection and analysis were performed using the TA Instrument Universal Analysis 2000 software (v. 4.5A). The linear peak integration function was used to determine the peak melting temperature (T_m).

Thermogravimetry (TGA) Analysis. TGA thermograms were recorded using a TGA Q500 from TA instruments Inc. The TGA was calibrated using a calcium oxalate monohydrate standard. Samples (~5.000 mg) were equilibrated at 25 °C for 5 min while heating at 5 °C/min to 250 °C (temperature accuracy of 0.1 °C) under N_2 atmosphere (60 mL/min). Data collection and analysis were performed with the TA Instrument Universal Analysis 2000 Software (v. 4.5A).

Gas Chromatography (GC). The solvent residual content was determined using the GC (Model 451) system coupled with a headspace sampler (Model 8400). The GC system equipped with a standard split/splitless injector (100:1 split ratio), a flame-ionization detector (FID) at 250 °C and a Rxi-624 Sil MS GC capillary column (30 m x 250 µm x 1.40 µm, Restek Corporation). The GC method was adopted from literature. (Rahman et al., 2018) The headspace syringe was initially inspected by recording the chromatogram of the empty syringe for ensuring the absence of MeOH. Sample of 1 mL for neat MeOH (reference) was transferred to the headspace 20 mL vials with screw caps (Agilent) followed by the injection of 10 µL using the headspace syringe (Model 7671, Hamilton). Nitrogen gas was used as a carrier gas at a flow rate of 1 mL/min. The content of one formulated capsule was transferred directly into the headspace before injection. The column was equilibrated at 35 °C for 5 min, followed by heating at 15 °C/min to 250 °C with a holding time of 2 min at the end. The total run time per injection was 21.33 min.

Drug Content. In this study, the drug content percentage (DC%) in the formulated CrySoD capsule refers to the measured drug content (m_{exp}) using UV–Vis spectroscopy relative to the target drug content (m_{set}) employing eq. (1). (Hill et al., 2009, Okwuosa et al., 2017)

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

In eq. (1), m_{exp} and m_{set} represent the measured and set mass (mg) of MOD, determined using eq. (2), (3), respectively:

$$m_{exp} = c_{exp} V_{diluted} \quad (2)$$

$$m_{set} = c_{set} V_{dispensed} \quad (3)$$

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where c_{exp} and c_{set} are experimentally measured and set MOD concentrations in solution (mg/mL). The c_{set} was determined based on the solubility data obtained in this work (Figs. 2b and S3), detailed in the results and discussion section below. $V_{diluted}$ is the diluted volume (mL) of analyzed capsule before UV–Vis measurements, and $V_{dispensed}$ the dispensed volume of MOD solution into the capsules during additive manufacturing. Preliminary tests proved no PEG interference with the MOD absorption (Fig. S5).

In this study, ten capsules (n = 10) containing CrySoDs were individually dissolved in 10 mL neat MeOH agitated at 700 rpm utilizing 20 mL scintillation vials temperature controlled at 50 °C. Once visually dissolved, the solution was filtered (PTFE syringe filter detailed above) into a 100 mL volumetric flask (PYREX) and diluted in MeOH. A volume of 0.1 mL of the resulting solution was further diluted in 50 mL (volumetric flask, PYREX) to obtain a target concentration of ≤ 10 µg/mL yielding absorbance measurements of < 1 using an offline UV–Vis spectrometer (Cary 100 Series, Agilent Technologies, temperature controlled at 20 °C) United States Pharmacopeia, 2020. All measurements were performed with a 200 – 600 nm scan and analyzed using the UV Cary Scan software (v. 200.470). The λ_{max} of absorbance for MOD in neat MeOH occurred at 220 nm. A linear calibration curve (R^2 = 0.999) was derived by measuring serial dilutions of a stock solution (1 mg/mL) shown in Fig. S6a. The calibration curve was used to determine the MOD concentration and calculate the weight needed to compute the drug content percentage (*DC*%) employing eq. (1). (Rodríguez-Maciñeiras et al., 2025, Hill et al., 2009).

Content Uniformity. The content uniformity of the 10 formulated capsules was assessed by evaluating the drug content variation for each unit dose United States Pharmacopeia, 2011 using UV–Vis spectroscopy. The acceptance value (*AV*) is calculated using eq. (4) United States Pharmacopeia, 2011:

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

where M represents the reference value (target dose, 100 mg in this study), $\bar{X}$ the mean of individual dose expressed as a percentage of the label claim, s the sample standard deviation (n = 10), and k the acceptability constant. According to USP, k = 2.4, if the number of unit doses is n = 10, as in this study United States Pharmacopeia, 2011.

Dissolution Studies. Dissolution profiles were measured for the generated capsules, commercial MOD tablet (100 mg, Provigil®, TEVA), and bulk MOD "as received" adapting the USP guidelines Park et al., 2024. Briefly, the dissolution experiments were conducted in a covered 3 L jacketed beaker (Chemglass, 200 mm inside diameter, 100 mm height) placed on a stirring plate (IKA C-MAG HS 7 Control model). The beaker was temperature-controlled at 37 ± 0.5 °C using a recirculating water bath (Lauda, RA 8). A thermometer was placed inside the beaker to record the temperature of the dissolution medium when samples are drawn. The dissolution studies were performed in 900 mL acidic medium (0.1 N HCl) (United States Pharmacopeia) under constant agitation at 100 rpm using a cylindrical magnetic stir bar (35 mm length, 8 mm diameter). Aliquots of 10 mL were withdrawn every 5 min and immediately filtered using a PTFE syringe filter (detailed above) before being analyzed without dilution using offline UV–Vis spectroscopy (detailed above). The MOD concentration was calculated by employing a MOD calibration curve in 0.1 N HCl obtained by serial dilutions of a stock solution (Fig. S7). The withdrawn aliquot volume was replaced immediately with fresh dissolution

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medium to maintain the total volume of acidic medium (Park et al., 2024). Dissolution profiles of generated capsules were conducted in sextuplet (n = 6) (Park et al., 2024) and for commercial 100 mg tablet (n = 1). The relative deviation (RD) and average relative deviation (ARD%) were used to compare the dissolution profiles between the reference Provigil® tablet and the formulated CrySoD capsules in this work employing Eqs. (5), (6).

$$RD = \frac{D_C^i - D_P^i}{R_C^i} \tag{5}$$

$$ARD\% = \frac{100}{N} \sum_{i=1}^{N} \left| \frac{D_C^i - D_P^i}{D_c^i} \right| \tag{6}$$

Where D_C^i and D_P^i are the ith experimental percentage dissolved MOD for the formulated capsule (this study) and Provigil® tablet (commercial), respectively, and N represents the total number of experimental values. In this study the experimentally determined percentage dissolved of Provigil® tablet was taken as the reference release rate to calculate RD and ARD%.

3. Results and discussion

3.1. THERMODYNAMIC DESIGN SPACE FOR CRYSOD

Understanding the thermodynamic design space of MOD, solvent, and polymer is essential for controlling the polymorphic form of MOD (Mbodji et al., 2024) in the novel CrySoD formulation approach while ensuring sufficient drug loading of 100 mg per unit (capsule) (Teva Pharmaceuticals). Therefore, in this study the standardized capsule sizes #000 was selected, which is a size patients can conveniently consume (Kabeya et al., 2020). Splitting the commercial dose of 100 mg into multiple capsules is less favorable (Caldwell and Raitt, 2010).

MOD can form seven polymorphic forms (I–VII), two hydrates, and two solvates (Mahieux et al., 2016, Ceausu et al., 2011, Mahieux et al., 2013). A prior publication revealed that among the solvents reported leading to the regulatory approved MOD form I (Mbodji et al., 2024) only MeOH and dimethylformamide (DMF) possess suitable temperature-dependent solubility characteristics, with ≥ 25 mg/mL between 5 and 60 °C (Mbodji et al., 2024). Although DMF exhibited a higher extrapolated MOD solubility than MeOH (517.5 mg/mL$_{Solvent}$ versus 78.7 mg/mL$_{Solvent}$ at 55 °C) (Mbodji et al., 2024) MeOH was selected as the formulation solvent. Both are class 2 solvents (Food and Drug Administration) which are less favorable than class 3 solvents for pharmaceutical applications (Smallwood, 1996). However, solubility and solid form control challenges required the use of a class 2 solvent (Urwin et al., 2020). Especially, MeOH is commonly used as an (anti)solvent in pharmaceutical processes (Brittain, 2009, Sangwal et al., 2007), while DMF is undesirable because of its toxicity and environmental impact (Alfonsi et al., 2008, Byrne et al., 2016). In addition, MeOH possesses a relatively

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low boiling point of 64.7 °C compared to DMF (153 °C) (Smallwood, 1996), which eases its removal by evaporation needed for the CrySoD formulation process reported in this study.

PEG is an FDA approved polymer excipient (Milton Harris and Chess, 2003), widely used to prepare CrySoDs (Mascia et al., 2013, Sanabria Ortiz et al., 2020, Mura et al., 1999, Zhu et al., 2012, Eloy and Marchetti, 2014), and considered as a green solvent in the molten state (Hoffmann, 2022). Both MOD and PEG are soluble in MeOH (Mbodji et al., 2024, Dinc et al., 2009). Several studies have reported solubility enhancement of APIs in the presence of PEG, acting as a cosolvent (Soltanpour et al., 2013, Rathi et al., 2018, Thimmasetty et al., 2020, Ha et al., 2017, Desai and Park, 2004, Le Khanh et al., 2023). In the CrySoD formulation approach presented in this study, PEG (MW 10,000 g/mol) was dissolved in MeOH forming a binary MeOH – PEG solvent system for MOD that may alter the APIs solubility compared to neat MeOH due to the presence of the hydrophilic polymer (Le Khanh et al., 2023). Consequently, first the solubility of PEG in MeOH was investigated before measuring the MOD solubility enhancement in the binary MeOH – PEG solvent system (Fig. 2).

Fig. 2a illustrates a strong temperature-dependent solubility of PEG in neat MeOH, indicating their interactions in solution (Schall and Myerson, 2019). At 35 °C the average PEG saturation concentration is 548.2 mg/mL$_{Solvent}$. This result is in agreement with literature reporting alcohols as qualitatively good solvents for PEG (Dinc et al., 2009, Desai and Park, 2004, Haglund, 1987, Kinugasa et al., 1994, D'souza and Shegokar, 2016). However, documented quantitative data are inconsistent not allowing for further assessment in this study (Dinc et al., 2009, Desai and Park, 2004, Haglund, 1987).

Thereafter, the solubility of MOD in MeOH as function of the PEG saturation concentration was measured (Fig. 2b). A scatter plot of the data is illustrated in Fig. S3. To the authors knowledge, to date no temperature-dependent MOD solubility data in the binary MeOH – PEG solvent system has been reported. Fig. 2b displays an increasing experimental MOD solubility with both increasing temperature and concentration of the hydrophilic polymer in the binary MeOH – PEG solvent system. Specifically, the MOD solubility increases from 78.7 mg/mL$_{Solvent}$ in neat MeOH to 104.0 mg/mL$_{Solution}$ in MeOH – PEG at 55 °C, representing a solubility improvement of 25.3 mg/mL (32.1 %). Thus, the MOD target concentration of 100 mg/mL$_{Solution}$ can be obtained at a lower temperature of 53.5 °C in the binary MeOH – PEG solvent system (Figs. 2b, S3, Table S2) compared to neat MeOH with a value of 63.4 °C (extrapolated using trendline in Fig. S3), which is closer to the MeOH boiling point of 64.7 °C (Smallwood, 1996). This MOD solubility enhancement in the binary MeOH – PEG solvent system is consistent with previous findings documenting improved solubility of MOD in aqueous solution containing low molecular weight PEG (Thimmasetty et al., 2020). Consequently, it was hypothesized that dispensing 1 mL of the MOD (c_{MOD} = 100 mg/mL$_{Solution}$) – MeOH – PEG (c_{PEG} = 548.2 mg/mL$_{Solvent}$) solution into a commercial capsule carrier, would deliver the commercial 100 mg dose of MOD (Teva Pharmaceuticals) embedded within a PEG matrix as a CrySoD upon solvent evaporation. These concentrations relate to a mass fraction of 15 wt% of MOD form I in 85 wt% PEG. PXRD analysis of the resulting solid obtained from the preliminary CrySoD tests confirmed the crystallization of MOD form I embedded in PEG (Fig. S10).

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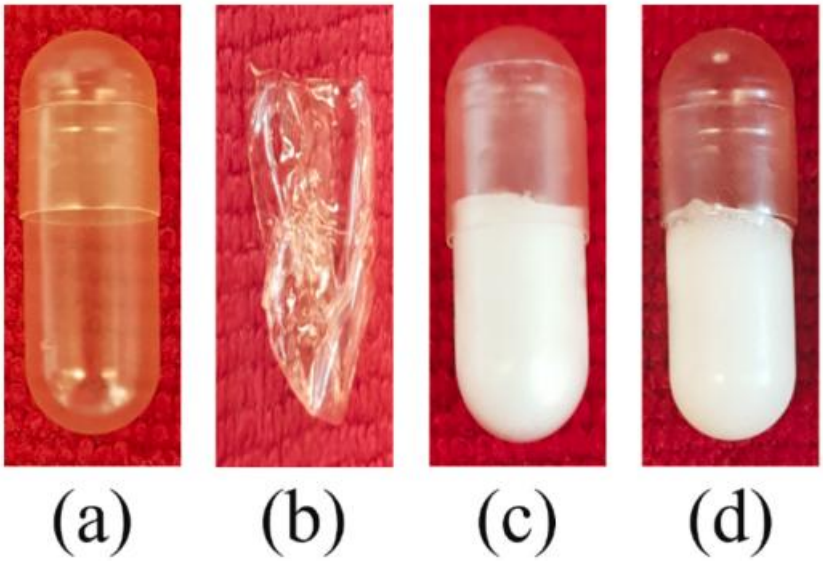
3.2. ADDITIVE MANUFACTURING OF MOD CAPSULES

Capsule Stability. Before conducting the additive manufacturing experiments, the stability and form integrity of the capsule carrier (Fig. 3a) needed to be tested in the presence of MeOH because HPMC, the capsule material, is reported to be soluble in most organic solvents, including MeOH. (Archer, 1992, Williams et al., 2001) It was hypothesized that the relatively low boiling point of MeOH (64.7 °C) (Smallwood, 1996) would lead to fast evaporation of 1 mL dispensed solution per capsule, thus, preventing the dissolution and disintegration of the capsules. The 1 mL volume was chosen based on the solubility data of MOD in MeOH – PEG solution (100 mg/mL$_{Solution}$, Fig. 2) to achieve a commercial 100 mg dose of MOD per capsule. (Teva Pharmaceuticals) However, despite an experimentally determined MeOH evaporation rate of 1.3 ± 0.1 mg/min in a ventilated-fume hood at ambient conditions (Fig. S8), the capsules were completely disintegrated within 1 h (Fig. 3b). In contrast, capsules recovered by evaporation of saturated MeOH – PEG (c_{PEG} = 548.2 mg/mL$_{Solvent}$) solutions (Fig. 2) did not show any visual signs of deformation (Fig. 3c) despite a slower evaporation rate of 1.0 ± 0.1 mg/min. This observation is caused by the presence of the solute PEG. (Roche et al., 2021) Similarly, MOD (c_{MOD} = 100 mg/mL$_{Solution}$) dissolved in this saturated solution MeOH – PEG, did not alter the stability of the capsule material (Fig. 3d). Details of the evaporation experiments (Hofmann, 1932) are provided in Section S4.

Fig. 3. Photographs of commercial HPMC capsules (size #000); (a) "as received" as well as after dispensing 1 mL of (b) neat MeOH, (c) MeOH saturated with PEG, c_{PEG} = 548.2 mg/mL$_{Solvent}$, and (d) MeOH – PEG with MOD, c_{MOD} = 100 mg/mL$_{Solution}$ (CrySoD of MOD form I). Capsules (b–d) were kept uncapped inside a ventilated-fume hood at ambient conditions for solvent evaporation ≥ 7 days. Once completed, capsules (c) and (d) were manually closed for the photographs.



These two noted effects of decreasing evaporation rate and diminished HPMC capsule disintegration in the presence of a solute (API, polymer) has been reported in the literature. (Marcus, 1993, Mabesoone et al., 2020) The former is caused by interactions between the molecules through, e.g., dispersive forces and hydrogen bonding, which result in changes of the evaporation rates. (Roche et al., 2021) Similarly, the presence of two polymers (in this study HPMC and PEG) in a solvent (e.g., MeOH) alters their interaction with the solvent, which likely inhibits the capsule dissolution and disintegration compared to neat MeOH. (Wolf et al., 2002) Specifically, it is documented that two

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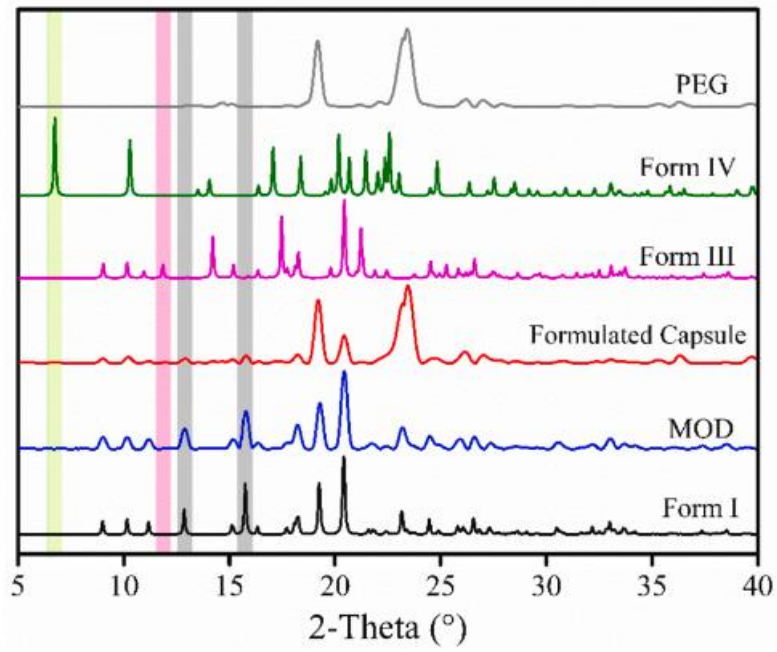
polymers not belonging to the same homologous series of polymers (e.g., HPMC and PEG), are incompatible in the same solvent, despite having high solubility in the same solvent when dissolved independently. (Dobry and Boyer-Kawenoki, 1946, Scott, 1949, Tompa, 1949).

MOD Solid Form Control. MOD can crystallize in multiple solid forms. (Broquaire et al., 2004, Mahieux et al., 2016, Mahieux et al., 2013, Stokes et al., 2014) The commercial MOD form I can be obtained by a cooling crystallization from MeOH (Broquaire et al., 2004, Silva-Brenes et al., 2024, Mbodji et al., 2024). Similarly, this study demonstrates that MOD form I can also be achieved and embedded within a PEG matrix, thus CrySoD (Chiou and Riegelman, 1971), by a controlled evaporative crystallization process (evaporation rate not claimed to be optimized, ≤ 1.1 ± 0.03 mg/min, Fig. S4 and S8) from a binary MeOH – PEG (c_{PEG} = 548.2 mg/mL$_{Solvent}$) solution (Figs. 4, S8, S9).

Fig. 4. Powder X-ray diffractograms (PXRD) of the simulated MOD form I (black, CCDC Reference Code = 236078); (Pei et al., 2004) form III (pink, CCDC Reference Code = 284321) (Pauchet et al., 2006), and form IV (green, Reference Code = 908057) (Mahieux et al., 2013) as well as experimental "as received" MOD form I (blue), formulated CrysSoD capsule after physically removing the capsule shell for PXRD analysis (red), and "as received" PEG (grey). Shaded areas in light grey, light pink and light green indicate the characteristic peaks for MOD form I, III and IV, respectively (Ceausu et al., 2011). Simulated diffractograms were extracted from crystallographic information files obtained from the Cambridge Structural Database (Groom et al., 2016). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



The absence of peaks other than for MOD form I in the capsule formulated CrySoD, including the known polymorphic forms III and IV (Mahieux et al., 2013, Pauchet et al., 2006), demonstrates high solid form purity (Fig. 4). This conclusion is drawn within the detection limit of the PXRD instrument employed in this study (Newman et al., 2015). Moreover, MOD form I was consistently obtained for different ratios (10–80 wt%) of MOD and PEG in MeOH as long as a slow solvent evaporation rate of ≤ 1.1 ± 0.03 mg/min was ensured. The data (PXRD, Raman spectroscopy, DSC, and TGA) for this assessment are illustrated in Figs. S10-S14. In contrast, accelerating the drying process by increasing the evaporation rate to e.g., ≥ 1.6 ± 0.2 mg/min by increasing the temperature to 40 °C, concomitant polymorphs (Bernstein et al., 1999, Lee et al., 2008) of MOD (form I, III, and IV) were observed, as depicted in the PXRD diffractograms (Figs. S9 and S16). Similar evaporation rate, thus supersaturation

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rate, dependent appearance of concomitant or undesired metastable polymorphs have been reported in the literature (Bernstein et al., 1999, Lee et al., 2008, Rafilovich et al., 2005, Wang et al., 2024). Generally, the formation of such mixed and metastable solid forms is typically due to competing kinetic and thermodynamic factors (Lee et al., 2008). Particular polymer solutions seem to be prone to the formation of concomitant and metastable polymorphs of APIs as evidenced in numerous publications in recent years (Sanabria Ortiz et al., 2020, López-Mejías et al., 2009, Prasad et al., 2016). This prevalence is likely caused by the reduced mass transfer of the solute API in the polymer solutions/melt compared to conventional neat solvents (Hernández Espinell et al., 2022, Sanabria Ortiz et al., 2020).

3.3. CRYSTALLINE SOLID DISPERSION CAPSULE ANALYSIS

After 7 days of storage (desiccator with P_2O_5 at ≤ 25 %RH and ambient temperature), representative capsules (Fig. 3d) were subjected to the product quality tests demanded for commercial MOD tablets (Provigil®) (United States Pharmacopeia). In addition, GC analysis confirmed that the representative capsules formulated in this study were free of solvent (MeOH) within the detection limit of the GC instrument (10–100 ppm, Fig. S15) (Yu et al., 2014, United States Pharmacopeia, 2007, Krupčík et al., 2015). Consequently, the amount of MeOH in each CrySoD capsule must be < 30 mg, the maximal permitted daily exposure (Food and Drug Administration).

Drug Content. The drug content is an important critical quality attribute of formulated drug products. (Yu et al., 2014) The additively manufactured CrySoD capsules needed to contain MOD in the amount of 100 mg/unit ± 10 % (United States Pharmacopeia) to compare to the commercial tablets (Provigil®) (Teva Pharmaceuticals) for the anticipated therapeutic effect. The results, summarized in Fig. 5 reveal high reproducibility with an average weight of 99.8 ± 0.8 mg and a DC% of 99.8 ± 0.8. Thus, the manufactured capsules in this study are within the USP acceptance criteria of 90–110 % for the MOD tablet (Provigil®) (Teva Pharmaceuticals, United States Pharmacopeia).

As a side note, in this study the DC% was determined using offline analytics (Guan et al., 2015, Qiu et al., 2024). However, process analytical technology (PAT) might also be possible. PAT has been documented for DC% calculation with the advantage of non-destructive *in situ* monitoring enabling advanced manufacturing for real time drug release (Romañach et al., 2023, Fontalvo Gómez et al., 2019). Though beyond the scope of this study, e.g., the application of NIR and Raman spectroscopy to monitor the solution concentration coupled with a load cell to measure the capsule weight as it is additively filled has been suggest to enable such a manufacturing approach with a high level of process control (Sundarkumar et al., 2022).

Content Uniformity. The content uniformity determines the proximity and difference between the average and the value of individual dose units and was evaluated using eq. (4) United States Pharmacopeia, 2011. However, following the USP recommendation based on the *DC%* = 99.8 obtained in this study, eq. (4). can be simplified to eq. (7) United States Pharmacopeia, 2011.

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

where k = 2.4 (acceptability constant) and s is the calculated sample standard deviation (s = 0.8 for 10 formulated capsules) United States Pharmacopeia, 2011. Hence, the capsule doses additively

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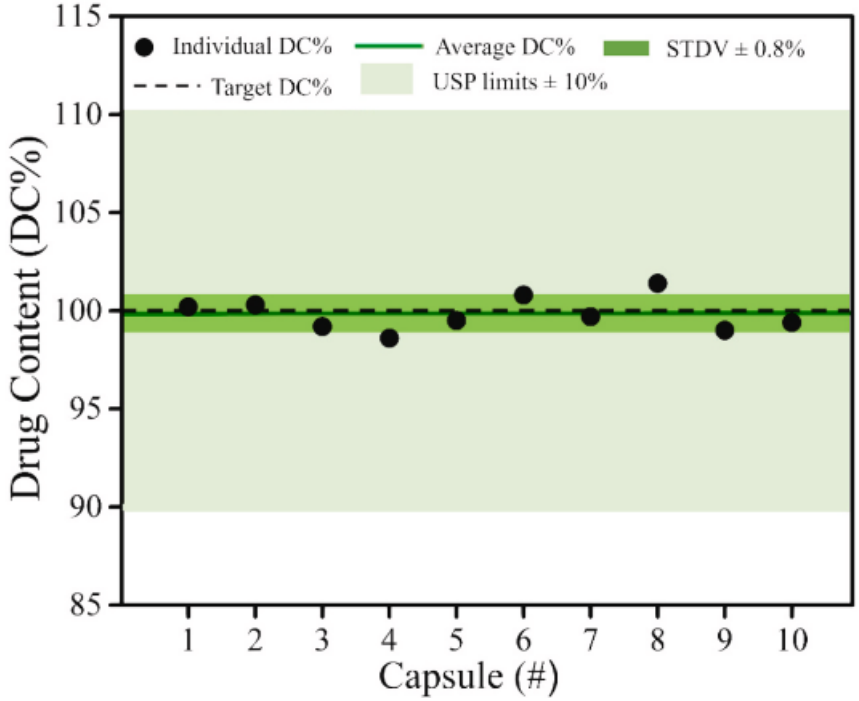
manufactured in this study result in an *AV* = 1.92, which is an order of magnitude smaller compared to the required USP *AV* of 15 for solid dosage formulations United States Pharmacopeia, 2011. Consequently, the presented capsule filling approach in this study enables high MOD drug loading with precise dosing, which can be attributed to the generally more accurate metering of liquids (e.g., solutions) compared to heterogeneous mixtures of suspensions or blends of solids needed, e.g., in tabletting Radcliffe et al., 2019.

Fig. 5. Drug content percentage (DC%) of individual dose units (n = 10, black solid data point) measured using UV–Vis spectroscopy. The green solid and black dashed lines indicate the average (99.8 %) and target (100 %) DC%. Dark and light green-shaded areas represent the standard deviation (STDV) of the MOD CrySoD capsules generated in this study (± 0.8 %) and the USP acceptance limits for MOD tablets (± 10 %) (United States Pharmacopeia), respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Dissolution Studies. Fig. 6 presents the dissolution profiles (percentage of drug dissolved over time) for the formulated MOD CrySoD capsules (both opened and closed), "as received" bulk MOD, and commercial Provigil® tablet. (Teva Pharmaceuticals) While comparing the dissolution profiles to bulk API is a good practice in formulation development, the commercial tablet serves as reference to assess the consistency and efficacity of the novel MOD CrySoD capsule formulation approach. (Kesisoglou and Wu, 2008) From Fig. 6 the formulated CrySoD capsules (closed) exhibited similar dissolution rates compared to the reference Provigil® tablet with an (ARD%) of 8.2. The main difference in the dissolution profile is caused by the initial delay within the first 5 – 10 min attributed to the time required for the capsule shell to dissolve (Radcliffe et al., 2019, Stegemann et al., 2014) (Fig. 6, insert). Thereafter, the drug dissolution rate increases and visually approaches that of Provigil® after 25 min. The capsule impact on the dissolution profile was further demonstrated by comparing open capsules (top of capsule was manually removed prior to experiment) with the Provigil® tablet resulting in an ARD% of only 3.8. Similar initial delays, though smaller, are caused by the remaining bottom part of the capsule shell. These findings suggest a capsule carrier-controlled release mechanism (Mehta, 1993) for the reported MOD CrySoD formulation approach. However, the polymer matrix itself does not alter

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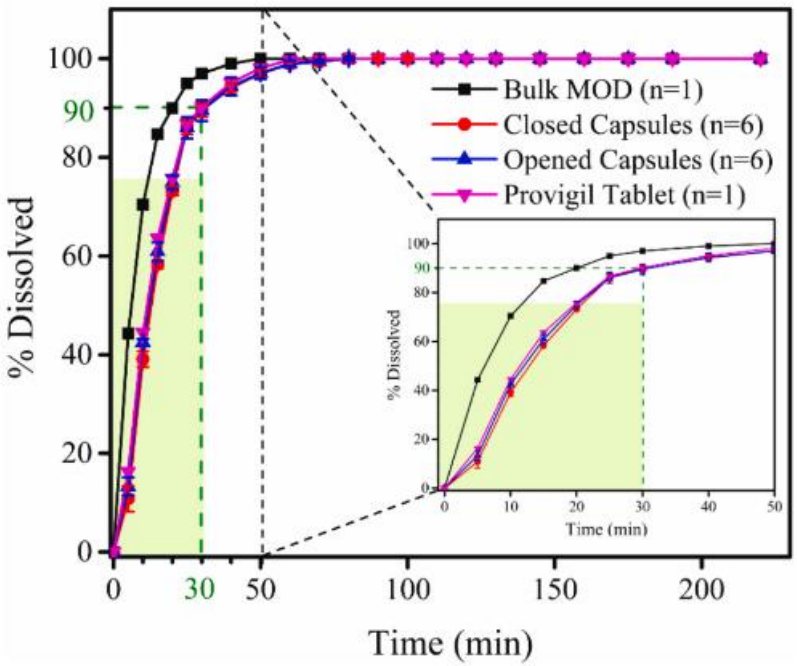
the dissolution characteristic as previously reported for similar solid dispersion systems. (Qiu et al., 2024, Lippold and Ohm, 1986, Vasconcelos et al., 2007, Lu et al., 2014, Castro et al., 2013, Craig, 2002, Lloyd et al., 1999) Notably, the capsules released ≥ 90 % of the drug within 30 min similar to the reference Provigil® tablet, indicating that both formulations meet the USP requirements for MOD tablets (≥ 75 % release at 30 min) (United States Pharmacopeia). Moreover, MOD CrySoD capsule achieved 100 % drug release within 60 min identical to the commercial MOD tablets (Teva Pharmaceuticals).

Fig. 6. Dissolution profiles of formulated "as received" bulk MOD (black), commercial Provigil® 100 mg tablet (pink), and MOD CrySoD capsules (closed [red] and opened [blue]). The insert emphasizes the negligible deviation between the capsules generated in this study and the Provigil® tablet. The green shaded area indicates the USP acceptance criteria of 75 % dissolved MOD amount within 30 min (United States Pharmacopeia). The green dashed line illustrates the achieved dissolution amount of 90 % of the formulated MOD CrySoD capsules in this study within 30 min. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



It is known that the API particle size alters the dissolution profile of a drug product (Eloy and Marchetti, 2014). Therefore, manipulating the particle size in conventional formulations are considered a critical CQA (Yu et al., 2014). However, determining the MOD crystal size and its distribution inside the solidified 3-dimensional polymer matrix of the reported capsule formulation approach is not trivial and beyond the scope of this study. As a vital aspect, a separate article is prepared detailing a non-destructive analysis for the API crystal size and its distribution within the additively manufactured capsules.

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4. Concluding remarks

This study reports a proof-of-concept for a liquid-based additive manufacturing approach to produce a solid dosage form, CrySoD, by dispensing a MOD – MeOH – PEG solution into capsules. Upon solvent evaporation, MOD crystallizes inside a solidifying PEG matrix within commercially available capsule shells used as carrier. By carefully selecting the solvent MeOH and determining the thermodynamic and kinetic boundaries of the evaporative crystallization process, capsules containing CrySoDs with polymorph control can be successfully produced. The CPPs, temperature, concentration, and evaporation rate altered the MOD solid form and properties of the CrySoD capsules. Evaporating the solvent at a rate of ≤ 1.1 ± 0.03 mg/min yielded the desired commercial form I. In this study, without claiming to be optimized, higher evaporation rates increased the propensity of concomitant polymorphs. The low acceptance value (*AV*) of 1.92 for the produced CrySoD capsules compared to the USP limit of 15 for solid dosage formulations demonstrate a high level of accuracy of the reported solid dosage manufacturing approach. This was further validated by the comparable dissolution profiles of the formulated capsule and commercial MOD tablets, Provigil® tablet (100 mg dose), used as reference. Accomplishing this proof-of-concept formulation platform marks an important milestone in a series of three publications that envision the development of mini plants for point-of-use pharmaceutical manufacturing away from the current mass production scheme, e.g., in remote areas or for personalized medicine. Consequently, the reported work might be used as a rationale for further studies as a potential solid dosage formulation platform (e.g., personalized dosing, technoeconomic analysis, regulatory science).

Moreover, the results presented in this study were achieved without claiming optimization of the thermodynamic design space of the liquid-based solid dosage formulation process. The focus was on demonstrating a target MOD concentration of c_{MOD} = 100 mg/mL$_{Solution}$, accomplished with c_{PEG} = 548.2 mg/mL$_{Solvent}$ at 35 °C. However, by extrapolating the trendline in Fig. 2a theoretical PEG concentrations of ~791 and ~1476 mg/mL$_{Solvent}$ at 40 and 50 °C, respectively, seem possible, suggesting further enhancement of the MOD solubility in the binary MeOH – PEG system for c_{PEG} > 548.2 mg/mL$_{Solvent}$ (Fig. 2b). Consequently, it might be possible to carry larger amounts of MOD while lowering the relative weight per unit dose.

Ultimately, this study presents a generalizable workflow and key insights into a novel formulation strategy as an innovative platform for solid dosage formulation. This platform eliminates the need for handling solids or generating a solid body, while also reducing the number of unit operations via process intensification. A solid dosage form can be achieved by identifying and controlling the CPPs to ensure the critical quality attributes (CQAs) are consistently met (Ulrich et al., 2011). The underlying concept is based on an evaporative crystallization process. As with any successful industrial crystallization process, a thorough understanding of the thermodynamic and kinetic design space of a specific system (here, API, solvent, polymer) is essential. Together with the CPPs of such a process, these factors govern the CQAs of the final product (Stelzer and Ulrich, 2010), e.g., solid dispersions with solid form control of the API whether crystalline or amorphous, depending on the application needs.

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Notes

The other authors declare no competing financial interest.

CRediT authorship contribution statement

Aliou Mbodji: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Kelitsha Mulero Cruz:** Writing – review & editing, Visualization, Formal analysis. **Andrea Arroyo Gomez:** 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. Romanach:** Writing – review & editing, Visualization, Formal analysis. **Torsten Stelzer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

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

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Appendix A. Supplementary material

The supporting information is available free of charge on the website. Characterization of physical mixtures of MOD and PEG detailed thermodynamic design space for CrySoD, formulated CrySoD capsules, determination of solvent evaporation rates, generation and characterization of CrySoD of MOD and PEG and recrystallization of MOD. Supplementary data to this article can be found online at https://doi.org/ 10.1016/j.ijpharm.2025.126197.

Data availability

Data will be made available on request.

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*The abbreviation CSD is commonly used in the pharmaceutical sciences and industrial Crystallization fields for two different meanings. To prevent confusion, in this work the abbreviation CrySoD is used for crystalline solid dispersion.

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