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# The challenge of downstream processing of spray dried amorphous solid dispersions into minitablets designed for the paediatric population – A sustainable product development approach

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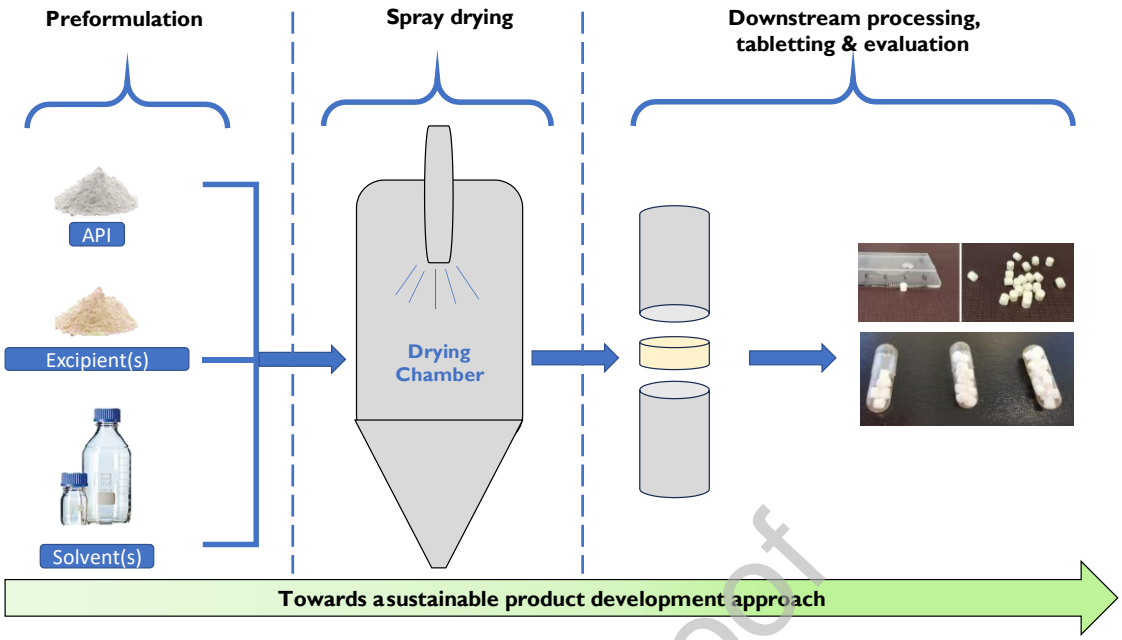
**Graphical abstract:**




**Highlights: (3-5 highlights,** maximum 85 characters, including spaces, per bullet point)

- Sustainable OSD design through the development of a versatile formulation to serve the needs of diverse patient populations
- Manufacturing minitablets of spray-dried amorphous dispersions is a challenge.
- Formulation development is required to improve flow into a small die orifice.
- Materials and manufacturing steps are minimised for efficiency and stability.
- A simple two-filler formulation was successfully developed for direct compression.

**Abstract**

Poorly water-soluble drugs present a significant challenge in the development of oral solid dosage forms (OSDs). In formulation development the appropriate use of excipients to adjust solubility, and the choice of manufacturing method and pharmaceutical processes to obtain a dosage form to meet the needs of the patient group, is crucial. Preparing an amorphous solid dispersion (ASD) is a well-established method for solubility enhancement, and spray drying (SD) a common manufacturing method. However, the poor flowability of spray dried

materials poses a significant challenge for downstream processing. Promoting sustainability in OSD development involves embracing a versatile formulation design, which enables a broader spectrum of patients to use the product, as opposed to altering existing dosage forms retrospectively. The objective of the current study was to develop a formulation of spray dried indomethacin ASD suited to the production, by direct compression, of instant release paediatric minitablets. Excipients evaluated were PVP or HPMCAS in solid dispersions at the preformulation phase, and MCC and lactose as a filler in direct compression. From the studied formulations, a 3:1 ratio blend of Vivapur 200/Pharmatose 200M (MCC/lactose) with 0.5 % (w/w) magnesium stearate was found to be the most promising in tableting, and minitablets containing a 6.22 % content of spray-dried ASD of indomethacin/PVP K 29-32 could be obtained with desired tablet hardness and pharmaceutical quality, complying with tests of weight variation and fast disintegration in an aqueous environment. As a case example, this study provides a good foundation for further studies in harnessing a sustainable approach to the development of pharmaceutical formulations that can appropriately serve different patient sub-populations.

Keywords: sustainability, spray drying, amorphous solid dispersion, preformulation, minitablets, paediatric dosage forms, downstream process

## 1. INTRODUCTION

Children are an underserved, vulnerable patient population for whom dosage forms with appropriate medication strengths, excipients and administration routes are often not commercially available (Lajoinie et al. 2016; Ivanovska et al. 2014). Further exacerbating the issue, poor aqueous solubility of the active pharmaceutical ingredient (API) poses complex challenges in the development of oral dosage forms suitable for children, especially given the pill burden associated with higher doses (Salunke et al. 2022). Adequate solubility is a critical API property because orally administered drugs must dissolve appreciably in the gastro-intestinal fluids to be absorbed. Moreover, with poor aqueous solubility being prevalent among new APIs, poor oral bioavailability may lead to overall larger doses of API being administered in an attempt to achieve an adequate amount to be absorbed (Lipp 2013, Yano et al. 2016). However, the unabsorbed fraction of the drug together with the eliminated fraction pose environmental risk when entering the environment via waste water. Large doses of API are a major contributor to the environmental burden of small molecule oral solid dosage forms (OSDs) (Schenck et al. 2024, Wang et al. 2021). Further environmental consequences of high dose API relate to API residues having been found to be hazardous to humans and animals alike, both when consumed directly as drinking water or through biomagnification occurring across the food chain (Majumder et al. 2019).

Compounding custom medicines for children from adult dosage forms is a common practice in pharmacies when suitable products are not available (Ivanovska et al. 2014). The quality assurance of these products, however, falls outside the rigor of being manufactured under a marketing authorization, and their formulation development is disjointed from that of the original product as well as the clinical trials associated with it. Paediatrically inappropriate excipients carrying over from the adult dosage form as well as the total excipient burden are also a concern (Fabiano et al. 2011). When compounding, resources and energy are expended to reformulate otherwise sales-ready products into paediatrically appropriate formulations, which is neither efficient nor sustainable. Introducing additional excipients when modifying the product negatively affects the process mass intensity, which is a measure of the efficiency of the conversion of raw materials into final pharmaceutical products (Jiménez-González et al. 2013).According to the PM9R framework , the resource and energy recovery benefits of a circular economy is best utilized through the design of multifunctional pharmaceutical products which reduces the need to repurpose, recycle or

recover materials or energy at a later stage in the product's life cycle (Ang et al. 2021). Correspondingly, rather than modifying existing dosage forms after the fact, *sustainability* is promoted by versatile formulation design that allows for the product to be used by a wider range of patients. Everything considered, ethically and ecologically sustainable alternatives for compounded paediatric medicines are needed, especially when involving drugs displaying poor aqueous solubility.

Minitablets made from an amorphous solid dispersion (ASD) of a poorly soluble drug address the issues of poor aqueous solubility, large drug doses and paediatric appropriateness (Zhang et al. 2020). ASDs are one of the possible approaches to improving a drug's apparent solubility, whereby the drug is transformed into an amorphous solid form, characterized by no long-range repeating patterns in orientation or distances between molecules, as opposed to the crystalline form in which there is a three-dimensional crystal lattice, composed of repeating unit cells (Van den Mooter 2012). In an ASD, the drug is evenly dispersed throughout a carrier, most commonly a polymer, which stabilizes the system by means of drug-carrier interactions, antiplasticization, molecular mobility reduction and nucleation activation energy augmentation (Duong et al. 2016). In this manner, the solubility of poorly soluble compounds can often be increased manyfold (Hancock and Parks 2000). The most suitable polymeric candidates for the API can be chosen at the preformulation stage of the ASDs production based on the individual properties of raw materials and their interactions (Tambe et al. 2022). ASDs can be manufactured through a range of methods of which spray drying (SD) and hot melt extrusion are the most common (Bhujbal et al. 2021). However, ASDs arising from these processes require further formulation and processing into a solid oral dosage form to optimize and control e.g., drug release, bioavailability, and stability. Examples of downstream processing of ASDs into tablets are readily found in both the academic literature and commercial applications (Bhujbal et al. 2021; Sauer et al. 2021; Sawicki et al. 2016). In contrast to regular sized tablets, cases of minitablets manufactured from ASDs are rare in the literature (Zhang et al. 2020). Minitablets have been cited as a promising dosage form for increased compliance in the treatment of children, the elderly and for veterinary use (Hejduk 2022; Savolainen et al. 2019; Thomson et. al 2009). Commonly quoted benefits of minitablets are their ease of administration and dose customizability through the adjustment of the number of minitablets. While some ambiguity exists as to their exact definition, minitablets are

generally regarded as tablets smaller than 4 mm in size (Kachrimanis et al. 2005; Lennartz and Mielck 1998; Pich and Moest 1989).

The objective of this study was to characterize and evaluate the suitability of excipients for the formulation of direct-compressed instant release 3.0 mm paediatric minitablets containing a spray-dried solid dispersion of indomethacin, as a model BCS Class II drug with low aqueous solubility (0.937 µg per ml at 25 ºC (Shakeel et al. 2013; Shi et al. 2019).

## 2. MATERIALS AND METHODS

### 2.1 Materials

The API, indomethacin (IND) (lot: D3NIJ) was purchased from Tokyo Chemical Industries (Tokyo Chemical Industries Ltd., Eschborn, Germany). The polymers, hydroxypropyl methylcellulose acetate succinate (HPMCAS MF (lot: 60F_71001), HPMCAS HF (lot: 65F_81003)) and polyvinylpyrrolidone (PVP K 29-32, (lot: 2348764)) were obtained from Ashland (Ashland Industries Europe, Meath, Ireland). Several grades of microcrystalline cellulose (MCC), brand name Vivapur®, was obtained from JRS Pharma (JRS Pharma GmbH & Co. KG, Rosenberg, Germany) and several grades of milled lactose monohydrate, brand name Pharmatose®, was purchased from DFE pharma (DFE pharma, Goch, Germany). Magnesium stearate and transparent hard gelatin capsules size 0 were obtained from University Pharmacy, Helsinki, Finland. Powdered beetroot (Beetroot Juice P-WS) was purchased from Sensient Food Colors (Sensient Food Colors Germany GmbH, Geesthacht, Germany). Ethanol was obtained from Scharlau (Scharlab, S.L, Spain), and in-house deionized water was used.

### 2.2. Preformulation of spray-dried amorphous solid dispersions

#### 2.2.1 Thermogravimetric analysis (TGA)

Samples were placed in aluminium pans and thermally analysed on a TGA (Q550, TA Instruments, Leatherhead, UK) using nitrogen purge gas (50 ml/min) by ramping the temperature at 10 °C/min over the 25 °C – 350 °C temperature range. The results were analysed in the TRIOS software (TA Instruments, Delaware, USA).

2.2.2 Differential Scanning Calorimetry (DSC)

Samples were weighed (5-10 mg), placed in Tzero aluminium pans, crimped with the lid with one pin hole and thermally tested on a DSC (Q2500, TA Instruments, Leatherhead, UK) using nitrogen as the purge gas (350 ml/min). The thermal events were evaluated by the TRIOS software (TA Instruments, Delaware, USA). All samples were subjected to a drying cycle prior to the thermal sequence by heating them up at 10 °C /min to 90 °C, holding them isothermally at 90 °C for 10 minutes, then equilibrating the temperature back to 25 °C.

2.2.2.1 Determination of the glass transition temperature (Tg) of API and mixtures of API and polymers

The glass transition temperatures of the API and mixtures of the API with each of the polymers were assessed by using a heat-cool-heat thermal sequence, in which the samples were heated over a temperature range of 25°C to 230 °C at the rate of 10 °C/min, held isothermally at 230 °C for 10 minutes, then cooled down to 25 °C at a rate of 50 °C/min, held there isothermally for 10 minutes, and finally heated again at 10 °C/min to 230 °C. The midpoint of the $T_g$was evaluated in all samples.

2.2.2.2 Determination of the glass transition temperature of spray-dried samples and polymers

Samples of polymer raw materials or spray-dried formulations were heated over a temperature range of 25°C to 230 °C at a rate of 10 °C/min. The midpoint of the $T_g$was evaluated in all samples.

2.3 Spray drying of API-polymer solutions

API and polymer powders were dissolved in 100 ml of solvent composed of 80% (v/v) ethanol and 20% (v/v) deionized water with total solute content of 3% (w/v), 5% (w/v) or 10% (w/v). Solutions were spray-dried using a ProCept spray-dryer (ProceptSD1, Zele, Belgium) equipped with a two-fluid nozzle with 0.4 mm nozzle tip and nitrogen as the atomizing gas in the closed mode. The process parameters were as follows: inlet temperature 120°C, cyclone gas flow 0.4 $m^3$/min, inlet gas flow 0.5 $m^3$/min, nozzle gas flow 10 L/min and feeding rate 5 g/min. The outlet temperature was observed to be at approximately 67 °C and the cyclone inlet temperature at 41 °C. Eight formulations consisting of either IND:PVP K 29-32 or IND:HPMCAS MF were spray dried using a large (L) cyclone size.

2.3.1 Determination of Process Yield

The yield was calculated by dividing the obtained weight (g) of processed powder by the total weight (g) of components initially subjected to processing.

2.3.2 Scanning Electron Microscopy (SEM) analysis

Prior to SEM analysis all samples were placed onto carbon tabs mounted on to aluminium stubs and coated with gold using a MP-19020N CTR sample coater (Deben UK Ltd., Suffolk, The United Kingdom) under vacuum conditions. Each coated sample was placed in the sample holder inside the SEM chamber. Images of raw materials and spray-dried systems were taken using a Jeol JCM 5000 NeoScope benchtop Scanning Electron Microscope (Deben UK Ltd., Suffolk, The United Kingdom) at the acceleration voltage range of 5-15 kV. Images were taken over the x900 – x1700 magnification range in various regions of the sample.

2.4 Flowability characterization

400 g of acclimatised excipient or powder blend was mixed in a Turbula shaker mixer (WAB-group, Muttenz, Switzerland) for 10 minutes (Table 1). Given the method of manufacture, SD-ASD particles were expected to be small. Different grades of different excipients were included to provide options for solving the anticipated issue of poor flowability. Flowability was tested by means of apparent/tapped volume based on which the Carr's indices and Hausner ratios were calculated (European Pharmacopoeia 2023). The temperatures and humidities recorded were between 21.6 °C and 23.1 °C, and 21.8% and 26.5% relative humidity.

Table 1. Excipients and excipient blends (consisting of excipients of different particle sizes) studied in the manufacture of minitablets. 0.5 % (w/w) magnesium stearate was added before minitablet manufacture. The numbering assigned to the grades is used for reference throughout this work.

| **Excipient * or excipient blend** | **Grade**** | **Filler ratios (w/w)** | **Average particle size or particle size combination / X10 – X90 particle size distribution** | **Blend No.** |
|---|---|---|---|---|
| MCC | 105 | N/A | 15 µm | 1 |
| | 101 | N/A | 65 µm | 2 |
| | 102 | N/A | 130 µm | 3 |
| | 200 | N/A | 250 µm | 4 |
| LAC | 200M | N/A | 40 µm (5 µm – 120 µm) | 5 |
| | 125M | N/A | 80 µm (30 µm – 140 µm) | 6 |

| | | | | |
|---|---|---|---|---|
| | 80M | N/A | 250 μm (70 μm – 390 μm) | 7 |
| MCC / MCC | 105 / 200 | 1 to 1 | 15 μm / 250 μm (small / large) | 8 |
| LAC / LAC | 200M / 80M | 1 to 1 | 40 μm / 250 μm (small / large) | 9 |
| MCC / LAC | 105 / 200M | 1 to 1 | 15 μm / 40 μm (small / small) | 10 |
| MCC / LAC | 105 / 80M | 1 to 1 | 15 μm / 250 μm (small / large) | 11 |
| MCC / LAC | 200 / 200M | 1 to 1 | 250 μm / 40 μm (large / small) | 12 |
| MCC / LAC | 200 / 80M | 1 to 1 | 250 μm / 40 μm (large / small) | 13 |
| MCC / LAC | 200 / 200M | 3 to 1 | 250 μm / 40 μm (large / small) | 14 |
| MCC / LAC | 105 / 80M | 1 to 3 | 15 μm / 250 μm (small / large) | 15 |

*MCC = Vivapur; LAC = Pharmatose. **Grade, average particle size and distribution according to general, non-batch specific product information provided by the respective manufacturers of MCC and lactose (JRS Pharma 2023; DFE Pharma 2023).

## 2.5 Mixing testing

Blend 14 was chosen as the base blend as it yielded the most promising placebo minitablets (see section 3) and the beetroot powder contents were chosen to be consistent with the projected ASD fractions of the minitablets. To determine the optimal mixing time, four formulations containing red beetroot powder were tested (see Table 2). 200 g of each powder formulation was prepared and two of the blends were pre-mixed by hand using geometric dilution. All blends were mixed in the Turbula mixer in five-minute increments for a total of 45 minutes of mixing time. At each five-minute interval, pictures were taken of the powder in the mixing jar for visual evaluation of homogeneity during mixing.

Table 2. The compositions of the test blends for mixing optimization.

| **Excipient** | **Mixing test Formulation 16** | **Mixing test Formulation 17** | **Mixing test Formulation 18** | **Mixing test Formulation 19** |
|---|---|---|---|---|
| Vivapur 200 | 75 % | 75 % | 75 % | 75 % |
| Pharmatose 200M | 18.75 % | 18.75 % | 12.5 % | 12.5 % |
| Beetroot colour | 6.25 % | 6.25 % | 12.5 % | 12.5 % |
| Pre-mixing | No | Yes | No | Yes |

2.6 Manufacture of minitablets

Prior to the manufacture of minitablets, 9.0 mm tablets were manufactured to screen out blends with inadequate flow. For the manufacture of minitablets, 3.0 mm single tip tablet punches (I Holland Ltd, Nottingham, United Kingdom) were fitted onto a rotary tableting machine (Ronchi Officine Meccaniche F.lli Ronchi s.r.l., Milan, Italy). The tableting machine was operated at slow compression setting (16.5 RPM) with the use of a gravity feeder. 100 g of each excipient powder blend was mixed for 10 minutes in the Turbula mixer after which 0.5 percent (w/w) of magnesium stearate lubricant was added before mixing for an additional five minutes. Two batches compressed at different average upper compression forces (~1000 N and ~1500 N) were manufactured from each blend. Target weight of 30 mg and target tensile strength of > 1 MPa for adequate durability during handling, storage and further processing were chosen (Kokott et al. 2021).

The minitablets were projected to contain $1/16^{th}$ to $1/8^{th}$ part SD-ASD which corresponds to 0.625 mg to 1.25 mg indomethacin for the ASD containing PVP K 29-32 (0.33 IND weight fraction). The initial target drug content has been set conservatively and can be increased if the minitablet quality criteria are met. For SD-ASD formulations, the powder blends were mixed for 20 minutes in the Turbula mixer with an additional 5-minute mixing time after the addition of the magnesium stearate. The room conditions observed were 21.6 °C – 23.1 °C and 21.8 – 26.5 % relative humidity.

2.7 Minitablet uniformity of mass, tensile strength and height

The uniformity of mass and crushing strength of the minitablets was evaluated according to the European Pharmacopoeia (European Pharmacopoeia 2023). An Erweka TBH 125 tablet hardness tester (Erweka Apparatebau GmbH, Langen, Germany) was employed to determine the crushing strength, from which tensile strength was calculated. The height was measured using a Sony digital micrometer (Sony Digital Indicator U30-F, Sony, Japan).

2.8 Disintegration

Disintegration tests were performed on both individual minitablets and hard size 0 gelatin capsules holding twelve minitablets. The disintegration tests (n=6) were conducted according to the European Pharmacopoeia, using purified water and a SOTAX DT3 manual

disintegration apparatus (SOTAX AG, Aesch, Switzerland)(European Pharmacopoeia 2023).

## 3. RESULTS AND DISCUSSION

### 3.1 Preformulation of spray-dried amorphous solid dispersions

The rationale behind the preformulation studies was to assess the individual properties of the materials used in the study, and their mixtures to identify the optimized blend for manufacturing ASDs by a spray-drying technique. Identifying differences between individual polymers' physical characteristics, their impact on the IND weight fraction used or the solubility in the solvent at an early stage of the process development leads to a data-driven selection of formulation components.

#### 3.1.1 Thermal analysis of raw materials and glass transition temperatures (Tgs) of API-polymer mixtures

In the current project, initial polymer candidate selection was based on the possible increase in the $T_g$ of a mixture of polymer with IND, so as to enhance the physical stability of the amorphous formulation. To this end, the polymers chosen in the study were HPMCAS MF, HPMCAS HF and PVP K 29-32, all characterized by a higher glass transition temperature ($T_g$), but also a higher degradation temperature and residual moisture content than the API raw material (Table 3). The thermograms of raw materials are presented in the supplementary material Figure S1 and **Error! Reference source not found.**.

Table 3. Residual moisture content and degradation temperature of API and polymer raw materials.

| Material | Indomethacin | HPMCAS MF | HPMCAS HF | PVP K 29 |
|---|---|---|---|---|
| $T_{g\ (midpoint)}$ (°C) | 39 | 124 | 124 | 160 |
| Residual Moisture Content (%) | 0.69 | 1.30 | 1.48 | 3.92 |
| Degradation Temperature (°C) | 244 | 270 | 273 | 320 |

In analyzing the $T_g$ of API-polymer mixtures, the intention was to identify the polymer weight fraction most suitable for generating an ASD system with a high $T_g$, and high drug loading, where the components would be still miscible with one another. To this

end, API was mixed with each polymer at a weight fraction from 0 to 1 and subjected to a melt quench (MQ) in the DSC to evaluate the impact of the type of polymer carrier and its weight fraction on the final critical quality attributes (CQAs) of the formulation, those being $T_g$ and heat of fusion.

The $T_g$s determined for the MQ samples are shown in Figure 1. The higher individual $T_g$ of PVP K 29 32 than that of HPMCAS polymers, resulted in higher $T_g$s of composite IND/ PVP K 29 32 melt-quenched mixtures. Even though different manufacturing methods may generate ASDs with different $T_g$s, the $T_g$ mostly relates to the individual weight fractions of components in the formulation and their respective $T_g$s; thus PVP-based ASDs are the preferred systems in this regard.

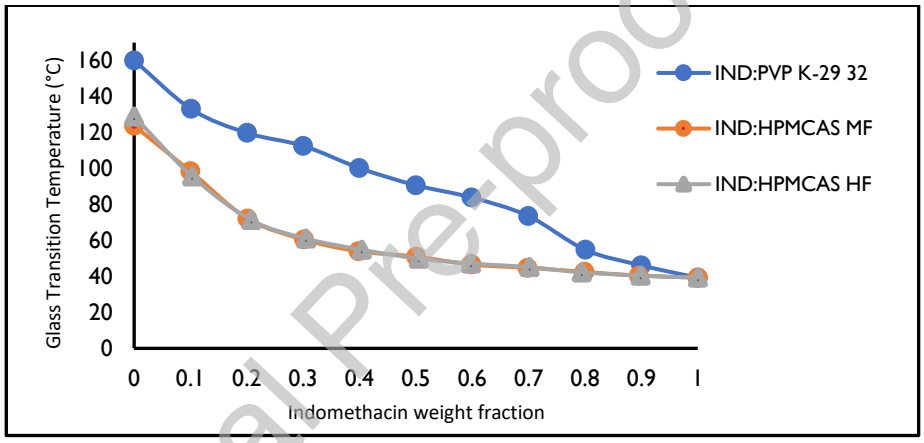



Figure 1. Glass transition temperature of melt quenched mixtures of API and polymers.

3.1.2 Heats of fusion of API-polymer melt-quenched systems

The other deciding factor in the choice of the polymeric matrix was an assessment of the possibility of ensuring the miscibility and solubility of API in the polymer carrier at high drug loading. In this study the heat of fusion of the pure crystalline material from the first DSC heating cycle of the crystalline API-polymer (Figure 2) was used to indicate the limit of IND weight fraction that might provide miscible ASDs systems.

The increase in heat of fusion of each IND/polymer combination was related to the increase in IND loading in the formulation. A steep incline was visible only from 60 % (w/w) IND loading in the IND/HPMCAS MF system and from 40% (w/w) IND loading in the PVP K29-32 system, indicating more miscible systems at lower drug loadings for these two polymers. This data led to the exclusion of the third system, IND/HPMCAS HF, from further

studies based on poorer drug-polymer miscibility. Even though the study of Tian et.al showed that the miscibility of IND with PVP is much higher than with HPMCAS (Tian et al. 2016), both HPMCAS MF and PVP K 29-32 were chosen for further processing with 0.20 and 0.33 IND weight fraction , and also 0.50 IND weight fraction for the PVP system, as these systems had both low heat of fusion and high glass transition temperatures.

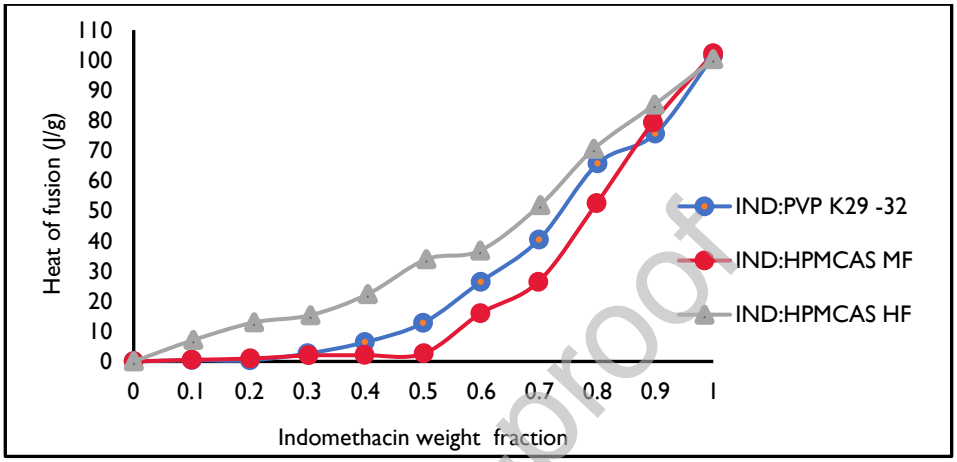



Figure 2. Heat of fusion of physical mixtures of API and polymers.

3.2 Characterization of spray-dried materials

All solutions of API-polymer were transparent and yellow in colour, and resulted in yellow, fine powders on spray drying (**Error! Reference source not found.**).

DSC analysis showed thermograms with a single $T_g$ indicative of a homogenous, miscible API/polymer phase with no endothermic peaks related to melting of crystalline IND evident, indicating the amorphous character of all spray dried formulations (**Error! Reference source not found.**). The $T_g$ of the spray-dried powders increased with an increase in the polymer content of the formulation, and was higher for the ASDs composed of IND/PVP K 29-32 compared to those containing HPMCAS (Table 4). By increasing the content of solute in solution, a subsequent increase in yield was observed in the systems with IND:PVP K 29-32 (from roughly 83% to 90%), however this was not observed with HPMCAS MF, as a fraction of material was lost on the spray-dryer drying chamber walls. As the $T_g$ of the composite API/polymer system is affected by the $T_g$s of the individual components and their ratio, spray-dried systems with HPMCAS were characterized by a lower $T_g$ at a higher polymer content than equivalent PVP systems, resulting in a more

rubbery character and greater adhesion to the spray-dryer walls at the chosen process conditions, with a subsequent decrease in yield.

Spray-dried materials with HPMCAS MF at 0.20 IND weight fraction and PVP K 29-32 at 0.33 IND weight fraction exhibited respectively higher and lower $T_g$s than their equivalent melt-quenched formulations, which is not surprising as the manufacturing method can impact the $T_g$ of ASDs. The divergence in $T_g$ of powders manufactured by different techniques can lead to different interactions of components at a molecular level, resulting in varied physical stability of the amorphous phase (Agrawal et al. 2013).

As IND loading increases, the glass transition reduces, which is in accordance with the Gordon-Taylor equation (Gordon and Taylor, 1952) which indicates that a higher weight fraction of the lower $T_g$ component results in a $T_g$ decrease for the ASD. Ueda et. al (Ueda et al. 2021) showed mostly negative deviations from the Gordon-Taylor equation for the IND-HPMCAS MG system, indicating the prevalence of homomolecular API/API or polymer/polymer interactions over heteromolecular API/polymer interactions. In contrast, for IND combined with various grades of PVP, experimentally obtained $T_g$s were more similar to those predicted by the Gordon-Taylor equation (Lopez et al. 2016, Yoshioka et al. 1995), indicating an absence of significant intermolecular bonds formation (Baghel et al. 2016). Further investigation of the interactions between components of spray-dried binary powders might be merited in future studies.

While the presence of polymer in a miscible mixture with the API increases the $T_g$ of the mixture, a trade-off should be made between the most optimal enhancement in physical stability indicated by this thermal parameter, API loading and the yield of the product.

Table 4. Characteristics of spray dried formulations.

| Sample number | Polymer | IND weight fraction (w/w) | Total solute content (% (w/v)) | Yield (%) | $T_g$ midpoint (°C) |
|---|---|---|---|---|---|
| **1** | PVP K 29-32 | 0.50 | 5 | 85 | 85 |
| **2** | **PVP K 29-32** | **0.33** | **5** | **91** | **100** |
| **3** | PVP K 29-32 | 0.33 | 3 | 83 | 99 |
| **4** | PVP K 29-32 | 0.33 | 10 | 90 | 101 |
| **5** | HPMCAS MF | 0.33 | 5 | 82 | 62 |
| 6 | HPMCAS MF | 0.20 | 5 | - | 81 |
| **7** | HPMCAS MF | 0.20 | 3 | - | 81 |
| **8** | HPMCAS MF | 0.20 | 10 | 75 | 78 |

Irrespective of the polymer type used, the SEM images taken presented spherically shaped spray-dried particles (Figure 3), as opposed to the large, irregularly shaped particles of IND and polymer raw materials (**Error! Reference source not found.**). The similar morphology of the spray-dried powders suggests that different polymers and solute concentrations used had no obvious effect on the drying kinetics of the process, often characterized by the dimensionless Peclet number (Sadek et al., 2015).

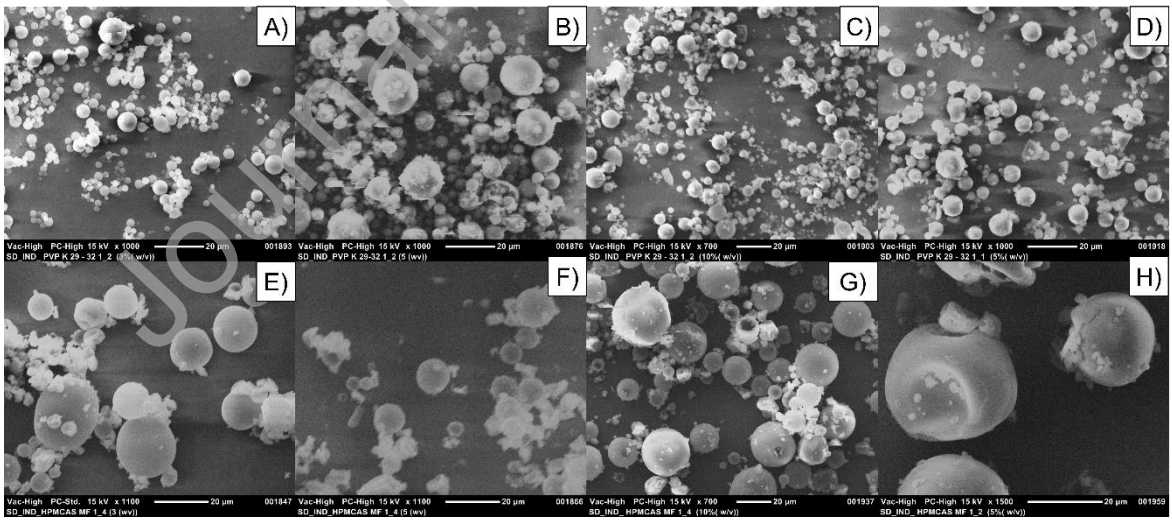



Figure 3. SEM images of spray-dried 1:2 IND: PVP K 29 -32, spray dried from solutions with A) 3% (w/v) B) 5% (w/v), C) 10% (w/v) total solute content and D) 1:1 IND: PVP K 29 -32 spray dried from a solution with 5% (w/v) total solute content, and 1:4 IND: HPMCAS MF spray dried from solutions with E) 3% (w/v) F) 5% (w/v), G) 10% (w/v) total solute content and H) 1:2 IND: HPMCAS MF spray dried from a solution with 5% (w/v) total solute content. Note: the scale bar on each SEM image is 20 μm.

From the eight initial SD-ASD candidates listed in Table 4, sample number 2 (IND:PVP K 29-32 1:2 spray dried from a 5% w/v solution) was chosen for minitablet manufacture based on a seemingly narrow particle size distribution and relatively well-defined, non-sticky particle surface interfaces, as observed on SEM images (Figures 3). Furthermore, for adequate stability, ASDs are usually stored at least 50 °C below their $T_g$ (Pandi et al. 2020). Therefore, candidates with a glass transition temperature below 70 °C were omitted from consideration on account of predictable stability issues at room temperature. Sample 2 has a high $T_g$ (100 $^oC$). In its final selection, the ease of manufacture, process yields and API loading were also considered.

3.3 Flowability

Carr's indices and Hausner ratios below 25 and 1.34, respectively, were obtained for the powder blends tested (Table 5). The ranking of the core excipients (No 1 to No 7) appears reasonable, with the Carr's indices and Hausner ratios decreasing as the average particle size increases. Excipient flowability is critical in the successful formulation of powders with a small average particle size, such as can be expected of spray dried indomethacin-polymer particles, as well as for minitablet manufacture in general (Krantz et al. 2009, Rumondor et al. 2016).

Based on this, Vivapur 200 and Pharmatose 80M were selected for binary combination (w/w) flowability testing because they had the best Carr's indices/Hausner ratios in the initial screening, and Vivapur 105 and Pharmatose 200M were selected for their small particle size, to emulate the size of indomethacin-polymer particles, while still maintaining a passable flowability. An argument for using particles with a large size discrepancy is that the smallest particles may adhere onto the largest particles, resulting in the overall flowability being governed by the better flowing larger particles (Thalberg et al. 2004). The binary powder blends of Vivapur 200/Pharmatose 200M and Vivapur 105/Pharmatose 80M were found to be the most promising combinations for successful tableting because they both displayed fair Carr's indices/Hausner ratios, consisted of a large particle size- and small particle size excipient as well as having both fragmenting and elastic deformation properties.

The Carr's indices and Hausner ratios obtained for the IND-PVP SD-ASD as well as blend No 14 containing 6.25 % or 12.5 % of the IND-PVP SD-ASD were below 25 and 1.34, respectively. According to these results, the flowability of the SD-ASD and powder blends with excipients were quite adequate.

Table 5. Carr's indices and Hausner ratios of excipients, excipient blends and blends containing the IND-PVP dispersion. Excipients marked with asterix (*) are core excipients consisting of only one excipient while all the others are excipient blends. (n=3)

| Flowability classification | Excipient | Carr's index (Av. of n = 3) | Hausner ratio (Av. of n = 3) |
|---|---|---|---|
| **Good**<br><br>Carr's index 11-15<br><br>Hausner ratio 1.12-1.18 | No 4: Vivapur 200 * | 11.9 ± 1.5 (SD 1.3) | 1.14 ± 0.018 (SD 0.02) |
| | No 14, retested: Vivapur 200/Pharmatose 200M, 3:1 ratio, 45 min mixing time | 13.5 ± 5.2 (SD 4.6) | 1.16 ± 0.070 (0.06) |
| | No 13: Vivapur 200/Pharmatose 80M, 1:1 ratio | 14.4 ± 2.2 (SD 1.9) | 1.17 ± 0.30 (SD 0.03) |
| | No 15: Vivapur 105/Pharmatose 80M, 1:3 ratio | 15.8 ± 0.12 (SD 0.1) | 1.19 ± 0.0016 (SD 0.00) |
| | No 14: Vivapur 200/Pharmatose 200M, 3:1 ratio | 15.9 ± 1.7 (SD 1.5) | 1.19 ± 0.024 (SD 0.02) |

| Flowability classification | Excipient | Carr's index (Av. of n = 3) | Hausner ratio (Av. of n = 3) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Fair**<br><br>Carr's index 16-20<br><br>Hausner ratio 1.19-1.25 | Spray-dried amorphous INDn dispersed in PVP K 29-32 (1:2 IND to polymer ratio) | 16.6 ± 1.01 (SD 0.89) | 1.20 ± 0.01 (SD 0.013) |
| | No 15, retested: Vivapur 105/Pharmatose 80M, 1:3 ratio, 45 min mixing time | 16.6 ± 1.8 (SD 1.6) | 1.20 ± 0.026 (SD 0.02) |
| | No 7: Pharmatose 80M * | 17.4 ± 1.6 (SD 1.4) | 1.21 ± 0.023 (SD 0.02) |
| | No 12, retested: Vivapur 200/Pharmatose 200M, 1:1 ratio, 45 min mixing time | 18.3 ± 1.2 (SD 1.1) | 1.22 ± 0.018 (SD 0.02) |
| | No 6: Pharmatose 125M * | 18.8 ± 1.1 (SD1.0) | 1.23 ± 0.017 (SD 0.02) |
| | No 3: Vivapur 102 * | 19.3 ± 1.3 (SD 1.2) | 1.24 ± 0.020 (SD 0.02) |
| | No 11: Vivapur 105/Pharmatose 80M, 1:1 ratio | 19.5 ± 1.8 (SD 1.6) | 1.24 ± 0.027 (SD 0.02) |
| | No 11, retested: Vivapur 105/Pharmatose 80M, 1:1 ratio, 45 min mixing time | 19.6 ± 0.21 (SD 0.2) | 1.24 ± 0.0032 (SD 0.00) |
| | 75 % Vivapur 200<br>12.5 % Pharmatose 200M<br>12.5 % Spray-dried amorphous INDn dispersed in PVP K 29-32 (1:2 IND to polymer ratio) | 19.6 ± 2.0 (SD 1.7) | 1.24 ± 0.03 (SD 0.03) |
| | No 5: Pharmatose 200M * | 20.2 ± 1.9 (SD 1.7) | 1.25 ± 0.030 (SD 0.03) |
| | No 10: Vivapur105/Pharmatose 200M, 1:1 ratio | 20.7 ± 0.55 (SD 0.5) | 1.26 ± 0.0089 (SD 0.01) |

| **Flowability classification** | **Excipient** | **Carr's index (Av. of n = 3)** | **Hausner ratio (Av. of n = 3)** |
|---|---|---|---|
| **Passable**<br><br>Carr's index 21-25<br><br>Hausner ratio 1.26-1.34 | No 2: Vivapur 101 * | 22.1 ± 1.8 (SD 1.6) | 1.28 ± 0.029 (SD 0.03) |
| | No 8: Vivapur 105/Vivapur 200, 1:1 ratio | 22.6 ± 0.33 (SD 0.3) | 1.29 ± 0.0055 (SD 0.00) |
| | 75 % Vivapur 200<br>18.75 % Pharmatose 200M<br>6.25 % Spray-dried amorphous IND dispersed in PVP K 29-32 (1:2 IND to polymer ratio) | 22.8 ± 1.14 (SD 1.01) | 1.29 ± 0.02 (SD 0.017) |
| | No 9: Pharmatose 200M/Pharmatose 80M, 1:1 ratio | | 1.30 ± 0.074 (SD 0.07) |
| | No 12: Vivapur 200/Pharmatose 200M, 1:1 ratio | 22.8 ± 4.4 (SD 3.9) | 1.30 ± 0.064 (SD 0.06) |
| | No 1: Vivapur 105 * | 22.8 ± 3.8 (SD 3.3) | 1.33 ± 0.0098 (SD 0.01) |

| | |
|---|---|
| | 25.1 ± 0.55 (SD 0.5) |



3.4 Mixing testing

Preliminary investigations whereby beetroot powder was substituted for the ASD indicated that adequate mixing and homogeneous powder blends were achieved after 20 to 25 minutes of blending in the Turbula mixer (See Figure S6). Given the recognised challenges associated with achieving content uniformity in minitablets, particularly at lower drug loadings, given their very small size, a precautionary pre-mixing step was introduced for the blend, prior to tableting (Mitra et al. 2020).

3.5 Manufacture of minitablets

The batches of placebo minitablets are listed in Table 6. 9.0 mm pre-testing led to blend No 11 being screened out due to inadequate flow. Tableting of a batch of blend No 15 with an average upper compression force near 1500 N was not attempted because of the large gap between the minimum and maximum upper compression forces when compressed at ~1000 N. Given that blend No 15 and blend No 11 both consist of Vivapur 105 and Pharmatose 80M albeit in a 1:3 and 1:1 ratio, respectively, it seems reasonable that both blends suffer from the same issues of poor flowability.

Table 6. Manufactured minitablet batches. 0.5 % (w/w) magnesium stearate was added.

| No | Formula | Composition ratio | Av. upper compression force (N) during 36 seconds | Min. and max. upper compression force (N) during 36 seconds | Av. crush. Strength (N) | Av. height (mm) | Batch |
|---|---|---|---|---|---|---|---|
| 4 | Vivapur 200 | N/A | 1080 | 1004 / 1164 | 62.6 | 3.262 | M4V200 |
| 12 | Vivapur 200<br>Pharmatose 200M | 1 : 1 | 1043 | 900 / 1152 | 53.7 | 3.301 | M10V200P200 |
| | | | 1407 | 1156 / 1660 | 60.7 | 3.228 | M14V200P200 |
| 13 | Vivapur 200<br>Pharmatose 80M | 1 : 1 | 1086 | 1008 / 1176 | 40 | 3.356 | M4V200P80 |
| | | | 1486 | 1388 / 1568 | 46.5 | 3.228 | M3V200P80 |
| 14 | Vivapur 200<br>Pharmatose 200M | 3 : 1 | 1057 | 988 / 1152 | 72.4 | 3.344 | M8V2P231 |
| | | | 1501 | 1436 / 1612 | 79.7 | 3.275 | M9V2P231 |
| 15 | Vivapur 105<br>Pharmatose 80M | 1 : 3 | 978 | 164 / 2240 | 32.4 | 2.155 | M3V1P813 |
| | Spray-dried amorphous indomethacin dispersed in PVP K 29-32 (0.33 IND weight fraction)<br>Vivapur 200<br>Pharmatose 200M | 1/16<br>12/16<br>3/16 | 994 | 956 / 1060 | 80.4 | 3.454 | 1AV2P231 |
| | | | 1539 | 1448 / 1640 | 80.3 | 3.287 | 2AV2P231 |
| | | 1/8 | 724 | 680 / 804 | 68.2 | 3.538 | 5AV2P231 |
| | | 6/8<br>1/8 | 1024<br>1506 | 965 / 1112<br>1420 / 1584 | 82.7<br>92.1 | 3.355<br>3.285 | 3AMV2P28<br>4AMV2P28 |

Based on the flowability results, the excipient composition No 14 (3:1 ratio of Vivapur 200 and Pharmatose 200M) was identified as a blend yielding tablets with sufficient tensile strength while also displaying adequate powder flowability, uniformity of mass, and suitable disintegration. This excipient blend was therefore selected as the basis for the manufacture of minitablets containing the SD-ASD of indomethacin and PVP K 29-32. The indomethacin-PVP tableting blends were created by replacing 25 % and 50 % of the Pharmatose 200M of blend No 14, which corresponds to one sixteenth or 6.25 % and one eight or 12.5 % of the total blend, with the SD-ASD. The rationale for this approach, was that replacing the small particle size Pharmatose 200M with the small particle size spray-dried ASD hopefully would cause the least change in the tableting behaviour and minitablet attributes.

Despite the challenging flowability, 3.0 mm minitablets were successfully manufactured from both powder blends containing 6.25 % and 12.5 % (before the 0.5 % magnesium stearate addition) of the indomethacin-PVP SD-ASD. Because of the yellow colour of amorphous indomethacin (Tanabe et al. 2012), the minitablets also have a light pale yellow colour (illustrated in Figure S7).

3.6. Uniformity of mass

For uncoated tablets weighing 80 mg or less, 90 percent of tablets must fall within a 10 percent mass deviation from the average mass (European Pharmacopoeia 2023). All placebo- and SD-ASD minitablet batches manufactured in this study met this requirement (Table 7 and Table S1), except for placebo batch M3V1P813 (Vivapur 105/Pharmatose 80M in 1:3 ratio). For SD-ASD minitablets, all weights recorded were within 2.37 % of the average minitablet mass of the sample, except for one outlying measurement at 4.73 % for batch 2AV2P231 (1/16 part ASD, ~1500 N compression).

Table 7. Recorded average, maximum and minimum minitablet weights (n = 20).

| **Batch** | **ASD content / compression** | **Average (mg)** | **Maximum (mg)** | **Minimum (mg)** | **SD (mg)** |
|---|---|---|---|---|---|
| 1AV2P231 | 1/16 / ~1000 N | 30.97 ± 0.191 | 31.57 | 30.33 | 0.43 |
| 2AV2P231 | 1/16 / ~1500 N | 30.54 ± 0.217 | 31.99 | 29.82 | 0.50 |
| 3AMV2P28 | 1/8 / ~1000 N | 29.61 ± 0.152 | 30.02 | 29.02 | 0.35 |
| 4AMV2P28 | 1/8 / ~1500 N | 29.69 ± 0.171 | 30.39 | 29.12 | 0.39 |
| 5AV2P231 | 1/8 / ~700 N | 30.12 ± 0.147 | 30.82 | 29.47 | 0.34 |

Figure 4 illustrates that the individual minitablet weight measurements are clustered rather well around their average values except for the one deviating measurement of batch 2AV2P231.

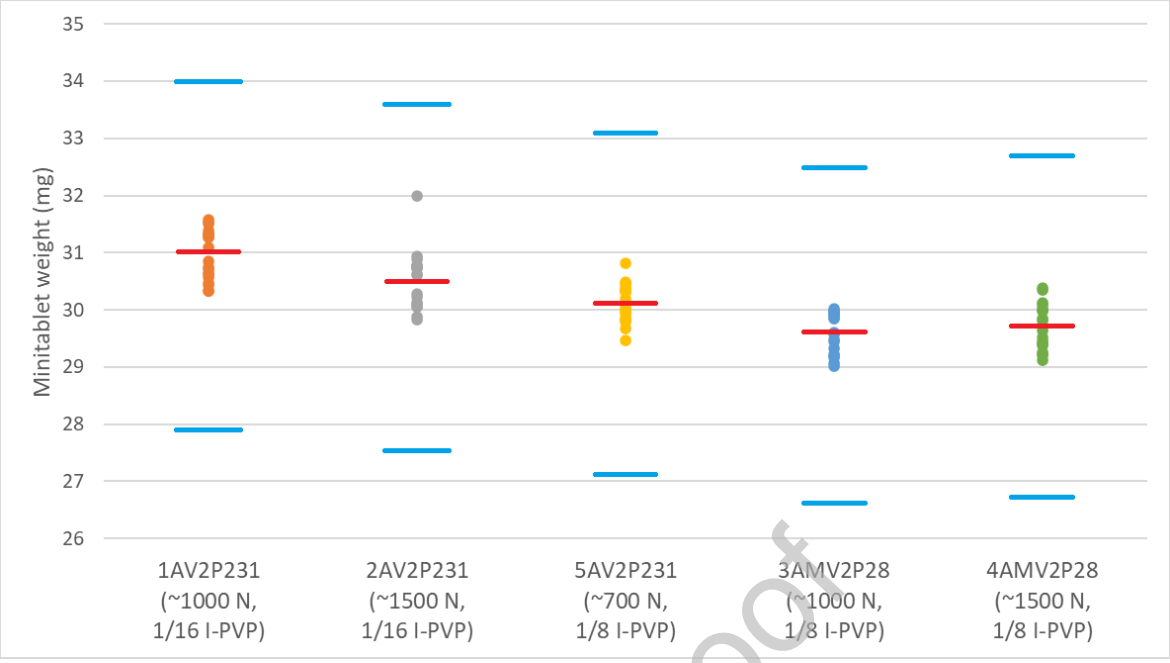



Figure 4. Individual indomethacin-PVP minitablet weights (n = 20) of batch. The average batch weight is marked with red and the ± 10 % weight limit from the average batch weight is market with blue.

In this context, the test for uniformity of mass was used as a screening tool. Mitra et al. found the weight variability of minitablets to be within ± 2 % (1.2 mm, 1.5 mm, 2.0 mm, 2.5 mm tablets) and ± 5 % (3 mm tablets) except for a few outliers (Mitra et al. 2017, Mitra et al. 2020). The weight RSDs were 0.7 – 3.0 % and ≤ 2.4 %, respectively. The mass variation findings for both placebo- and indomethacin-PVP minitablets of this study similar to the outcomes reported by Mitra et al.

3.7 Tensile strength and height

The tensile strengths of the minitablets comprised of SD-ASDs is illustrated in 5. Both the minitablets containing 1/16$^{th}$ and 1/8$^{th}$ indomethacin-PVP SD-ASD were very hard with average tensile strengths between 4.66 ± 0.19 MPa (SD 0.30, average compression force ~700 N) and 6.85 ± 0.19 N (SD 0.31, average compression force ~1500 N). While very few similar studies exist in the literature, these values are higher than described by others. Zhang et al. 2020 reported a tensile strength of ~2 MPa for 2 mm minitablets containing ASD of one of two undisclosed APIs with either PVPVA or HPMC (Zhang et al. 2020). Higher values were reported by Lavan et al. for 2 mm minitablets containing an ASD of lapatinib

and either HPMC E3 or hydroxypropyl methylcellulose phthalate, for which a tensile strength range of 3.3 ± 0.7 MPa to 4.0 ± 0.8 MPa was measured (Lavan et al 2021).

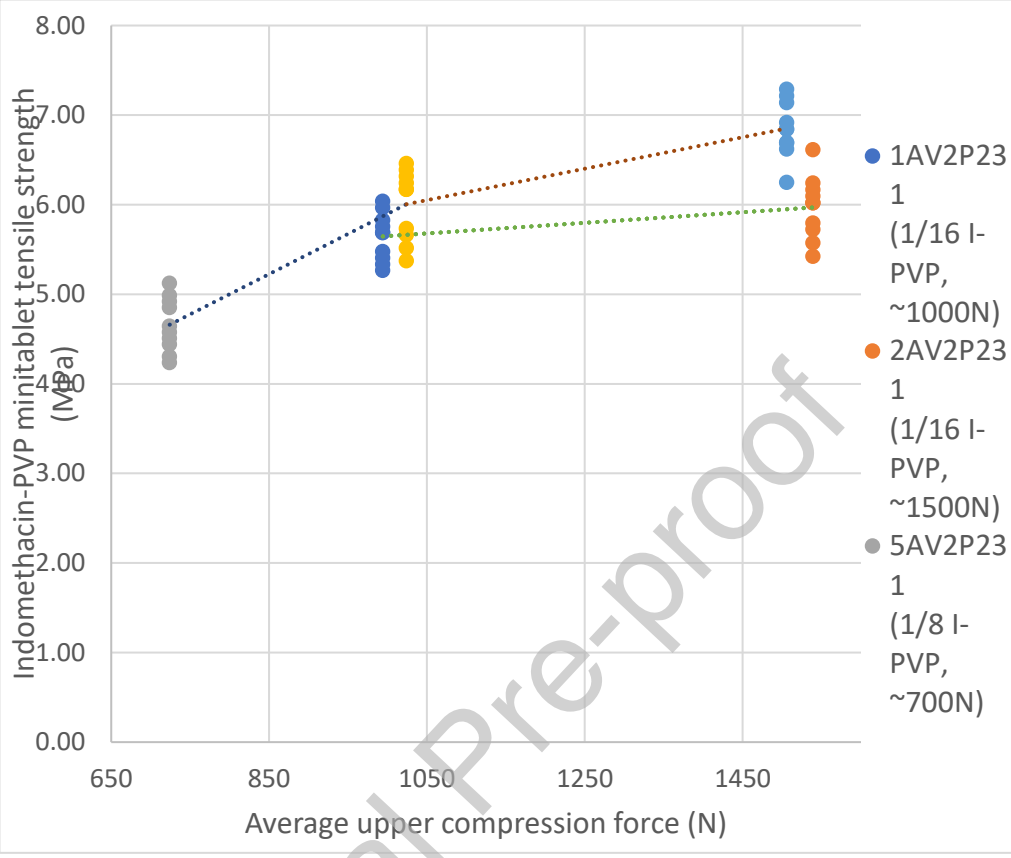



Figure 5. Indomethacin-PVP minitablet compression force and tensile strength relationship between batches prepared from the same powder blend (n = 10). The dotted lines represent a linear regression line between the data sets.

The average tensile strengths for the indomethacin-PVP minitablets comprised of 1/16$^{th}$ indomethacin-PVP dispersion (batch 1AV2P231 and 2AV2P231) were 5.65 ± 0.16 MPa (SD 0.27, average compression force ~1000 N) and 5.97 ± 0.22 MPa (SD 0.35, average compression force ~1500 N), respectively. For the indomethacin-PVP minitablets containing 1/8$^{th}$ of the SD-ASD, the corresponding values are 4.66 ± 0.19 MPa (SD 0.30, average compression force ~700 N), 6.00 ± 0.24 MPa (SD 0.39, average compression force ~1000 N), 6.85 ± 0.19 N (SD 0.31, average compression force ~1500 N). Compared to the corresponding blend No 14 placebo minitablets, which had average tensile strengths of 5.28 ± 0.21 MPa (SD 0.35) (batch M8V2P231, average compression force ~1000 N) and 5.95 ± 0.22 MPa (SD 0.36) (batch M8V2P231, average compression force ~1500 N), the tensile

strength appears to increase with increasing indomethacin-PVP content, although the confidence intervals overlap.

In addition to being a carrier in ASDs, PVP is a binder in tablet direct compression which may partially account for the hardness observed (Kurakula and Rao 2020). For the minitablets containing 1/8$^{th}$ part SD-ASD the PVP content of the overall formulation is 8.3 % (w/w), which is well above the normal range of 0.5 to 5 % PVP when PVP is used as a binder (Hiremath et al. 2019). The inclusion of the ASD material in the tablets is also a likely contributor to the hardness of the minitablets, although more research is needed in this area.

The average IND-PVP minitablet heights (n = 5) recorded were between 3.285 ± 0.046 mm and 3.538 ± 0.054 mm.

### 3.8 Disintegration

The single minitablet disintegration results are summarized in Table 8. All individual placebo minitablets fully disintegrated within three minutes (See Table S2 and S3) thereby complying with pharmacopoeia requirements for uncoated tablets (European Pharmacopoeia 2023).

Table 8. Disintegration times of six individual minitablets. 1AV2P231 and 2AV2P231 contain 1/16 part ASD at ~1000 and ~1500 N compression. 5AV2P231, 3AMV2P28 and 4AMV2P28 contain 1/8 part ASD at ~700, ~1000 and ~1500 N compression, respectively.

| **Batch** | **Average disintegration time (min) (n = 6)** | **Maximum disintegration time (min) (n = 6)** | **Minimum disintegration time (min) (n = 6)** | **SD** |
|---|---|---|---|---|
| 1AV2P231 | 3.52 ± 0.68 | 4.43 | 1.98 | 0.85 |
| 2AV2P231 | 5.04 ± 0.68 | 6.63 | 4.15 | 0.84 |
| 5AV2P231 | 7.87 ± 0.84 | 9.75 | 6.75 | 1.04 |
| 3AMV2P28 | 15.45 ± 1.72 | 17.28 | 11.98 | 2.14 |
| 4AMV2P28 | 14.14 ± 1.55 | 17.97 | 12.92 | 1.94 |

All individual minitablets containing 1/16$^{th}$ part SD-ASD fully disintegrated within 15 minutes. However, of the batches containing 1/8$^{th}$ of the SD-ASD, only batch 5AV2P231 compressed at ~700 N complied with this requirement.

In the literature, only one previous study investigating the disintegration of uncoated minitablets containing an ASD was identified (Lavan et al. 2021). These 2 mm minitablets contained an ASD of lapatinib and either HPMC E3 or HPMCP. Other excipients were MCC, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. At 2 % croscarmellose sodium Lavan et al. recorded an average disintegration time of 24 minutes, which is similar to the longest disintegration results of this study, however, without the use of a disintegrant. Other authors have found the disintegration times of minitablets containing an API in the crystalline form and a disintegrant to be less than a minute (Freerks et al. 2020, Mitra et al. 2020). It appears that the ASD increases the disintegration time of minitablets considerably, but given the sparse availability of research further studies are required to establish this relationship.

The disintegration times of capsules containing twelve minitablets is displayed in Table 9. It is noteworthy that the pharmacopoeia requirement for disintegration time for capsules is 30 minutes, which was met well in all cases in the present study. No studies of minitablet disintegration from gelatin capsules were identified for comparison. Figure S7 illustrates the filling of minitablets into gelatin capsules.

Table 9. Disintegration times of twelve minitablets in gelatin capsule (n = 6) 1AV2P231 and 2AV2P231 contain 1/16 part ASD at ~1000 and ~1500 N compression. 5AV2P231, 3AMV2P28 and 4AMV2P28 contain 1/8 part ASD at ~700, ~1000 and ~1500 N compression, respectively.

| **Batch** | **Total average disintegration time (min)** | **SD** | **Minitablet (12) average disintegration time (min)** | **SD** | **Capsule average disintegration time (min)** | **SD** |
|---|---|---|---|---|---|---|
| 1AV2P231 | 7.16 ± 0.35 | 0.43 | 5.43 ± 0.35 | 0.44 | 1.73 ± 0.28 | 0.35 |
| 2AV2P231 | 9.24 ± 0.60 | 0.75 | 7.62 ± 0.60 | 0.75 | 1.62 ± 0.14 | 0.18 |
| 5AV2P231 | 14.7 ± 0.63 | 0.79 | 13.1 ± 0.57 | 0.71 | 1.58 ± 0.16 | 0.20 |
| 3AMV2P28 | 20.1 ± 0.79 | 0.98 | 18.4 ± 0.97 | 1.21 | 1.65 ± 0.35 | 0.44 |
| 4AMV2P28 | 23.6 ± 1.46 | 1.82 | 21.9 ± 1.44 | 1.79 | 1.66 ± 0.19 | 0.24 |

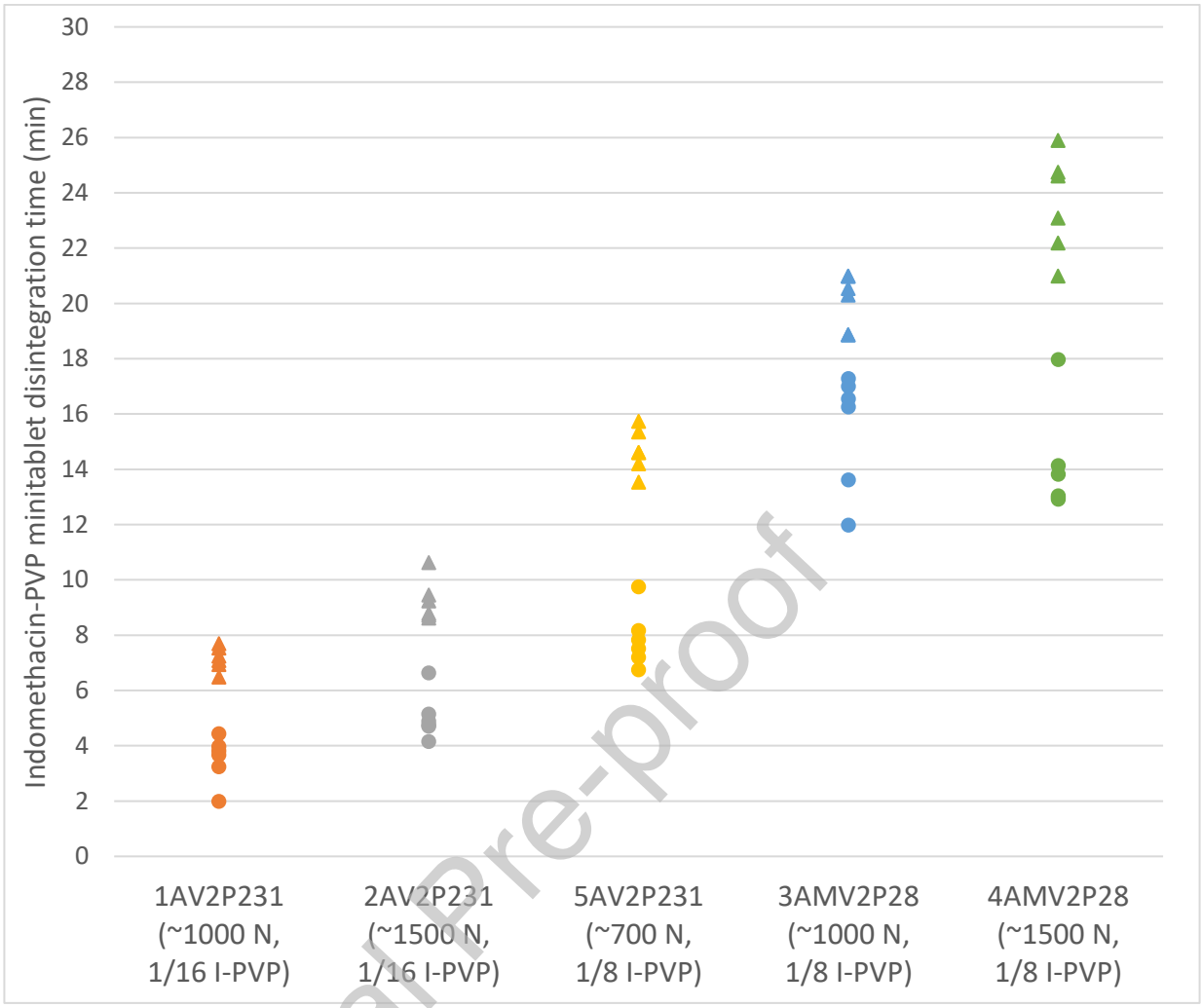



Figure 6. Disintegration times of minitablets containing 1/16$^{th}$ or 1/8$^{th}$ part IND-PVP SD-ASD(n = 6). Dots signify the disintegration times of individual minitablets, and triangles indicate disintegration times of size 0 gelatin capsules containing twelve minitablets.

When comparing the disintegration times of single minitablets and twelve minitablets filled into capsules (see Table 8 and Table 9), the average disintegration time increases considerably with the addition of the capsule (Figure 6). The slow minitablet disintegration upon being filled into capsules could be caused by the disintegration behaviour/mechanism. The SD-ASD minitablets disintegrated by snapping into 2 – 3 relatively large, persistent fragments which tended to lump together in a mass of gelatin and/or become glued to the discs/metal mesh of the container

Based on the data presented, a versatile minitablet formulation was designed which allows for flexible dosing for a wider range of patients, including children. Thereby, resources and energy expended in compounding paediatric medicines can be conserved and the carry-over of unsuitable excipients into the paediatric formulation avoided. Improving

the accessibility of poorly soluble APIs to the paediatric population advocates for the availability of adequate paediatric treatment options, ultimately promoting equality and sustainability in healthcare.

## 4. CONCLUSIONS

In this study, 3 mm minitablets containing $1/16^{th}$ and $1/8^{th}$ (w/w) of an amorphous solid dispersion of poorly water-soluble indomethacin with PVP K 29-32 were developed. Of the compositions tested, an excipient base comprised of a 3:1 ratio of large particle size MCC and small particle size lactose as well as 0.5 % (w/w) magnesium stearate was found to yield minitablets of excellent mass variability and acceptable strength. Instant release was achieved for both individual minitablets and hard gelatin capsules containing 12 minitablets. The information currently available in the academic literature regarding the downstream processing of spray-dried ASDs into tablets and especially minitablets is limited. This study demonstrated that when formulating the tableting powder blend for a small die orifice, minitablets complying with the defined specifications could be manufactured from a spray-dried ASD, despite its poor flowability. Secondly, minitablets as a dosage form are compatible with achieving instant release of API from solid dispersions, both as individual tablets and when administered in a capsule. As a case example, this study provides a good foundation for further studies in the development of minitablets from a spray-dried ASD. Direct compression of poorly flowing spray-dried indomethacin was achieved, thereby avoiding additional energy consuming manufacturing steps such as granulation, milling and drying processes. A simple minimal excipient, two-filler formulation which could be tabletted by direct compression was successfully developed. Such simple formulations illustrate a sustainable product development approach, with the formulation design enabling the production of final OSD products suited to a wide range of patients. While the emphasis in the current work has been on the development of an OSD formulation that can be used in products for diverse patient populations, future work is required to examine the sustainability and environmental impact of the manufacturing process employed and the raw materials utilized.

CRediT authorship contribution statement

Anja Autzen Virtanen, Monika Myślińska, Atif Madi: Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original Draft, Visualization; Eoin Power: Methodology; Anne Marie Healy, Atif Madi, Mia Sivén: Conceptualization, Methodology, Writing – Review & Editing, Resources, Supervision

## Declaration of Competing Interest

The authors declare that there is no competing interests related to this study.

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