



## Research paper

# Spray drying ternary amorphous solid dispersions of ibuprofen – An investigation into critical formulation and processing parameters

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## ARTICLE INFO

## Keywords:

Spray drying  
Ibuprofen  
Ternary formulations  
Amorphous solid dispersion  
Design of experiments  
Dissolution rate

## ABSTRACT

A design of experiment (DoE) approach was used to investigate the critical formulation and processing parameters in spray drying ternary amorphous solid dispersions (ASDs) of ibuprofen. A range of 16 formulations of ibuprofen, HPMCP-HP55 and Kollidon VA 64 were spray dried. Statistical analysis revealed the interrelation of various spray drying process conditions and formulation factors, namely solution feed rate, inlet temperature, Active Pharmaceutical Ingredient (API)/excipients ratio and dichloromethane (DCM)/methanol (MeOH) ratio. Powder X-ray diffraction analysis (PXRD) showed that all the samples with the lowest API/excipient ratio (1:4) were amorphous, while others were crystalline. Moreover, differential scanning calorimetry (DSC) analysis was employed to investigate ASD formulation more in-depth. The glass transition temperatures ( $T_g$ ) of all ASDs were in the range 70–79 °C, while crystalline formulations displayed an endothermic peak of melting of crystalline ibuprofen in the range of 50–80 °C. The high  $T_g$  of ASDs was an indication of highly stable ASD formulations as verified via PXRD at zero day and afterward at 1, 1.5, 3 and 6 month intervals. The intermolecular interactions between ibuprofen molecule and excipients were studied by Fourier transform infrared spectroscopy (FTIR) and solid-state nuclear magnetic resonance (ssNMR) spectroscopy. FTIR and Carbon-13 ssNMR analysis indicated that hydrogen bond formation involving the carboxyl group in ibuprofen within the ASDs is likely. More importantly, the solubility of ibuprofen in ASD formulations is improved compared to pure ibuprofen. This was due to both the amorphous structure of ibuprofen and of the existence of amphiphilic excipient, Kollidon VA 64, in the formulation.

## 1. Introduction

Approximately 40% of newly developed drugs are poorly water soluble or lipophilic in nature [1]. Poor solubility of newly developed Active Pharmaceutical Ingredients (API) is one of the major challenges that the pharmaceutical industry has been facing over the last two decades. Sekiguchi et al. [2] reported the development of solid dispersions by incorporating highly soluble phase or carrier (hydrophilic) for enhancing the dissolution of poorly water soluble drugs (hydrophobic). Since then, the use of solid dispersions (SDs) has been under investigation as one of the key strategies for improving the dissolution rate of poorly water soluble API. Amorphous solid dispersions (ASDs) depict high dissolution rates due to their highly disordered structure and higher Gibbs free energy compared to crystalline materials [3]. However, the inherent thermodynamic instability of the amorphous materials often leads to the relaxation, nucleation and crystal growth of the API during storage [4,5]. Thus, inclusion of amorphous polymeric

carriers can enhance the stability of the ASD formulations by either assembling new bonds with API molecule [6] or exerting an anti-plasticizing effect due to their high glass transition temperature ( $T_g$ ) [7].

Several technological approaches have been introduced for preparing ASD formulations including spray drying (SD) [8,9] and hot melt extrusion (HME) [10]. Spray drying is one of the most commonly used techniques due to its advantageous capability in continuous, rapid, scalable and controllable particle manufacturing when compared to other technologies [11–13].

Ibuprofen is a BCS class II anti-inflammatory drug with poor solubility being widely used in the market for more than 30 years. Binary ASDs of ibuprofen have been studied in the literature [14,15], however ternary ASDs have previously been reported to be superior to binary systems of other APIs in regard to their solid state stability and dissolution rate [16–18]. To date ternary ASDs of ibuprofen, their stability and dissolution properties have rarely been reported upon in the literature. This is possibly due to the low  $T_g$  of pure ibuprofen

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(−44.10 °C) thereby making it significantly more challenging to formulate as a stable ASD [19]. Although there are reports available for spray drying of ibuprofen with other excipients such as mesoporous SBA-15 [20] or silica [21] to enhance its solubility, none of these studies use a systematic approach to study physical and chemical properties of the final product. Thus, Design of Experiment (DoE) approach can be used to systematically screen, optimize and identify the critical and non-critical process and formulation factors [22].

This study aims to develop and optimise the spray drying process for producing ternary ASDs of ibuprofen with Kollidon VA 64 and HPMCP-HP55 as a novel formulation. The DoE approach was employed to optimise the effect of formulation and process parameters on the final properties of the ASD powders. It reveals a systematic approach to the optimised spray drying strategy of ternary ASDs using a comprehensive DoE. This methodology is helpful in optimizing the formulation, process factors and characterizing ASDs and can be implemented in formulating other ternary ASDs.

## 2. Materials and methods

### 2.1. Materials

HPMCP-HP55®, Kollidon VA 64®, and Soluplus® were donated by, Shinetsu, Ashland and BASF, respectively and racemic mixture (RS)-ibuprofen was purchased from Phion chemicals Co. Dichloromethane (DCM) and methanol (MeOH) were both purchased from Sigma Aldrich.

### 2.2. Methods and characterisation

#### 2.2.1. Design of experiments (DoE)

A design of experiments (DoE) was used to investigate the effect of various formulation and process parameters on the final properties of the powders. In this regard, a JMP® custom DoE module was used to devise a set of experiments. Five factors were selected to be studied, namely, solid content (5–15 w/v%), feed rate (2–10 mL·min<sup>−1</sup>), inlet temperature (70–85 °C), DCM/MeOH (1:3, 1:1 and 3:1) and API/excipients ratio (1:4, 1:2 and 2:3). It should be mentioned that the ratio of the excipients (HPMCP-HP55 and Kollidon VA 64) was kept at 1:1 for all compositions. Final yield, residual solvent content, particle size distribution, density, phase structure and morphology were analysed after spray drying. Table 1 shows the experimental design matrix.

**Table 1**

Experimental design matrix which shows the input parameters that were set for spray drying different samples (solid content, feed flow rate, inlet temperature, DCM/MeOH ratio, and API/excipient ratio).

|    | Solid content (w/v%) | Feed flow rate (mL·min <sup>−1</sup> ) | Inlet temperature (°C) | DCM/MeOH | API/Excipient |
|----|----------------------|----------------------------------------|------------------------|----------|---------------|
| 1  | 5                    | 10/3                                   | 70                     | 1:3      | 2:3           |
| 2  | 5                    | 40/12                                  | 70                     | 3:1      | 2:3           |
| 3  | 10                   | 25/7.5                                 | 77.5                   | 1:1      | 1:2           |
| 4  | 15                   | 40/12                                  | 85                     | 3:1      | 1:4           |
| 5  | 5                    | 40/12                                  | 70                     | 3:1      | 2:3           |
| 6  | 15                   | 40/12                                  | 85                     | 1:3      | 2:3           |
| 7  | 5                    | 10/3                                   | 85                     | 3:1      | 1:4           |
| 8  | 15                   | 10/3                                   | 70                     | 1:3      | 1:4           |
| 9  | 10                   | 25/7.5                                 | 77.5                   | 1:1      | 1:2           |
| 10 | 5                    | 10/3                                   | 85                     | 1:3      | 1:4           |
| 11 | 5                    | 40/12                                  | 85                     | 1:3      | 1:4           |
| 12 | 15                   | 10/3                                   | 70                     | 3:1      | 2:3           |
| 13 | 15                   | 10/3                                   | 85                     | 3:1      | 2:3           |
| 14 | 5                    | 10/3                                   | 85                     | 1:3      | 2:3           |
| 15 | 15                   | 40/12                                  | 70                     | 1:3      | 1:4           |
| 16 | 5                    | 40/12                                  | 70                     | 3:1      | 1:4           |

#### 2.2.2. Spray drying

The solubility of all components in different solvent ratios (DCM/MeOH; 1:1, 1:3 and 3:1) was checked visually to confirm the homogeneity of the solution. All samples were spray dried by a Büchi B-290 mini spray dryer. The inert loop was enabled in conjunction with a condenser at −20 °C to facilitate the use of organic solvents. The solid particles were collected by a high efficiency cyclone. A 2-fluid nozzle with 0.7 mm cap was employed for atomizing the solution of ibuprofen and excipients. Due to the volatile nature of organic solvents nitrogen was selected as the atomizing gas with flow rate of ~473 NL·h<sup>−1</sup> ( $P = 1013.25 \text{ mbar}$  and  $T = 273.15 \text{ K}$ ) and the aspirator was set to 100% (35 m<sup>3</sup>·h<sup>−1</sup>) for circulating nitrogen as drying gas. Collected powders were transferred to a desiccator immediately after production until further analyses.

#### 2.2.3. Thermal analysis

The residual solvent of all spray dried samples was analysed using a TGA-4000 Thermogravimetric Analyser (Perkin-Elmer Instruments, Beaconsfield, Bucks, UK) using heating rate of 10 °C·min<sup>−1</sup>. Nitrogen was used with 30 mL·min<sup>−1</sup> flow rate as instrument and balance purge gas.

A PerkinElmer DSC 8500 equipped with a refrigerated cooling accessory (PerkinElmer, Workingham) using helium (30 mL·min<sup>−1</sup>) as the purge gas was used to study the solid state of the spray dried samples. The instrument was calibrated at heating rates of 20 and 100 °C·min<sup>−1</sup> using high purity indium and zinc to standardise the temperature and heat flow signals. Samples (~5.0 mg) were weighed and placed in crimped DSC pans, then ramped from 20 to 200 °C at either 20 °C·min<sup>−1</sup> to check for crystallinity or 100 °C·min<sup>−1</sup> to study the glass transition regions. Analysis was carried out using PE Pyris Thermal Analysis software, version 10.1.

#### 2.2.4. Powder X-Ray diffraction (PXRD)

Spray dried powders were analysed using an X'pert PRO X-ray diffractometer (PANalytical, Almelo, the Netherlands) with monochromatized Cu K $\alpha$  radiation ( $\lambda = 0.15405 \text{ nm}$ ) attached to a computer running High Score Plus. The employed X-ray generator setting was 40 kV and 40 mA. Data were collected over the  $2\theta$  range of 5–50°, with a step size of 0.02 °·step<sup>−1</sup> and a step time of 40 s·step<sup>−1</sup>.

#### 2.2.5. Scanning electron microscopy (SEM)

The morphology of the spray dried particles was investigated by high resolution field emission electron microscopy (SEM, Hitachi SU-70) operating at 5 kV with 15 mm working distance. To avoid over-charging of the samples they were coated with gold-palladium for 2 min with 20 mA current.

#### 2.2.6. Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of the samples was measured at ambient temperature using a Perkin-Elmer Spectrum 100 FTIR spectrometer. The spectrum was collected at wavelengths of 4000–650 cm<sup>−1</sup> using an attenuated total reflection (ATR) accessory with a ZnSe crystal. Samples were placed on the crystal with a pushing arm and 128 scans were collected for each sample at a resolution of 4.00 cm<sup>−1</sup>.

#### 2.2.7. Solid state Nuclear Magnetic Resonance (ssNMR) spectroscopy

Carbon-13 NMR spectra were acquired on a Bruker Avance III HD NMR spectrometer operating at  $B_0 = 9.4 \text{ T}$ , with corresponding <sup>1</sup>H and <sup>13</sup>C resonance frequencies of  $\nu_0(^1\text{H}) = 400.1 \text{ MHz}$  and  $\nu_0(^{13}\text{C}) = 100.6 \text{ MHz}$ . Samples were packed in 4 mm o.d. zirconia rotors with Kel-F caps under ambient atmosphere, and experimental <sup>13</sup>C NMR spectra were acquired at natural abundance using a 4 mm double channel (X/H) Bruker MAS probe. NMR spectra were referenced to TMS at  $\delta_{\text{iso}} = 0 \text{ ppm}$  by setting the high frequency <sup>13</sup>C resonance in adamantane to 38.48 ppm [23]. The <sup>13</sup>C NMR spectra were acquired in a single spectral window using the cross-polarization pulse sequence,

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