

# Preparation and Evaluation of Pirfenidone Dry Powder by Spray Drying Technology

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**Abstract:** Inhalation of pirfenidone is one of the possible methods for effective treatment of idiopathic pulmonary fibrosis. In this study, we attempted to prepare inhaled pirfenidone dry powder through reasonable design of the precursor formulation and parameter adjustment of the spray drying process. The mechanism of polyvinyl alcohol (PVA) polymer as surfactant is used to assist the dissolution of pirfenidone in water, instead of using organic solvents (such as ethanol and methanol) for dissolution, so as to reduce the production explosion-proof requirements and avoid safety problems that may be caused by solvent residues. Leucine is first enriched and crystallized on the surface of particles and then condenses into a hydrophobic shell which collapses to form wrinkles to reduce the cohesion between particles. When the solvent is water, pirfenidone: polyvinyl alcohol: leucine=2:1:3, and the inlet temperature is 120 °C, the content of the active pharmaceutical ingredient (API) in the particles is 40.7%, and the relative content reaches 81.4% with a fraction of fine particles (FPF) of 26.2%, which represents good drug loading and inhalation performance.

## 1. Introduction

Pirfenidone (PFD) is a new pyridinone compound with broad-spectrum anti-fibrosis effect, which can prevent and reverse the formation of fibrosis and scar (Pardeshi 2021). Pirfenidone tablet was first launched in 2008 by SHIONOGI of Japan, and has been approved by the US Food and Drug Administration. It is the first drug that has been proved to have certain curative effect on idiopathic pulmonary fibrosis (IPF) through repeated, randomized, placebo-controlled phase III clinical trial (Richeldi 2011). At present, the main dosage form of pirfenidone is oral capsule. The adverse side effects such as first-pass effect and systemic toxicity caused by oral administration indicate the limitations of the capsule dosage form. To avoid or reduce the drawbacks of oral administration, inhalation dosage forms have become the direction of development. The inhalation dosage form is still in the experimental and clinical stage, including inhaled solution and inhaled dry powder.

Yoshiki Seto and Gen Suzuki successfully prepared PFD inhaled dry powder in 2016 by dissolving PFD with ethanol and adding leucine through spray drying (Yoshiki 2016). Ethanol used as a solvent is flammable and explosive, requiring explosion-proof equipment and workshops, which poses safety risks during experiments

and actual production and is not conducive to large-scale production. In addition, the residual organic solvent will also bring risks to the use of drugs by patients. In this work, polyvinyl alcohol (PVA) solution is used to assist the dissolution of pirfenidone in water, so as to avoid the risks caused by the use of organic solvents (Brough 2016, Sharipova 2017). At the same time, PVA, as a polymer, can provide a delayed release effect for PFD in the lung (Guo 2021).

The purpose of this paper is to use spray drying technology to prepare safe, controllable and stable pirfenidone particles. The microstructure of the particles was controlled by adjusting the precursor solution formulation and spray drying parameters. Various dry powder particle characterization techniques were used to observe the particle properties and optimize the conditions based on the results, and eventually the pirfenidone dry powder particles with best critical quality attributes (CQAs) were prepared.

## 2. Materials and methods

### 2.1 Materials

United States Pharmacopeia (USP) PFD was purchased

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from Vanz Pharm Co., Ltd. (Hubei, China) and Laifu Technology Development Co., Ltd. (Shandong, China). Poly (vinyl alcohol) (USP) was purchased from Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). L-leucine (USP) were purchased from Titan Technology Co., Ltd. (Shanghai, China). Distilled water used in all steps was produced from a Milli-Q device (~18.2 MΩ cm).

## 2.2 Preparation of the Feed Solution and SD Particles

The feed solution composition was shown in Table 1. In this study, organic solvents should be avoided to prepare the feed solution. Therefore, in order to make pirfenidone soluble in water, a certain amount of PVA should be dissolved in water first to make a solution to achieve the solubilization effect. After adding a certain amount of pirfenidone dissolved in water to get a clear solution. Leucine is then added to the precursor formulation. Leucine is easy to enrich at the air-solvent interface, and its low solubility makes it reach suoversaturation quickly at the beginning of spray drying, thus forming a hydrophobic shell on the surface of dry droplets nucleation. During the drying process, with the evaporation of solvent, the leucine on the surface of the droplets cannot shrink rapidly, resulting in the collapse of the surface layer and forming the outer surface of the fold. Therefore, adding leucine can effectively improve the aerodynamic properties of particles (Ordoubadi 2021, Zhang 2017). The abbreviation meaning in the formulation name is respectively: the first value represents the inlet temperature of the solution after atomization into the spray tower during spray drying; The subscript values of PFD, PVA and L represent the mass ratio of the three; The following MeOH or H<sub>2</sub>O indicates the solvent used, and the concentration of methanol solution was 20%; the last digit represented the total solid content of the feed solution.

## 2.3 Methods

### 2.3.1 Particle Size Distribution

The particle size distribution results were measured by laser diffraction using the Sympatec HELOS system equipped with the INHALER module (Sympatec GmbH, Clausthal-Zellerfeld, Germany) based on the static light scattering theory. The dispersion pressure of the powders was 4 bars, and the dispersion agent was compressed air. The instrument was simulated by Breezhaler® (Novartis, Swiss) with a single capsule size of about 10 mg (Figure 1). The two needles at the end of the device would pierce the capsule. During the inhalation process, the capsule rotated, vibrated or swung to release its drug, and the drug powder would collide at high speed between the powder particles and the mesh. The particle size distribution was calculated by the FREE model of the instrument pre-setting algorithm.



Figure 1: The schematic diagram of Breezhaler® dry powder inhaler

### 2.3.2 Scanning Electron Microscopy (SEM)

The morphology of the powder was characterized by scanning electron microscope (SEM, S-4700, Hitachi Hit-tech Co., LTD., Japan, Figure 2). The acceleration voltage of SEM is 15 kV and the image magnification is 800-20000 times. Before observation, the conductive carbon belt was fixed on the sample preparation table, and appropriate sample powder was placed on the conductive carbon belt and loaded into the ion sputtering coater (MC1000, Hitachi Co., LTD., Japan). Finally, the powder was sputtered and platinized to make the surface sample have electrical conductivity and avoid electric charge when observed under scanning electron microscope.

Table 1: Precursor formulation and process parameters for spray drying

Sample	PFD: supplement	PVA: L	Solvent	Total solid content /%wt	Inlet temperature /°C
130-PFD <sub>1</sub> PVA <sub>0</sub> L <sub>1</sub> -MeOH-0.5	1:1	—	MeOH	0.5	130
120-PFD <sub>1</sub> PVA <sub>0</sub> L <sub>1</sub> -MeOH-0.5	1:1	—	MeOH	0.5	120
130-PFD <sub>2</sub> PVA <sub>1</sub> L <sub>3</sub> -H <sub>2</sub> O-0.5	1:2	1:3	H <sub>2</sub> O	0.5	130
120-PFD <sub>2</sub> PVA <sub>1</sub> L <sub>3</sub> -H <sub>2</sub> O-0.5	1:2	1:3	H <sub>2</sub> O	0.5	120

Table 2: Particle size distribution under different formulations

Sample	D <sub>10</sub> /μm	D <sub>50</sub> /μm	D <sub>90</sub> /μm
130-PFD <sub>1</sub> PVA <sub>0</sub> L <sub>1</sub> -MeOH-0.5	6.07±0.70	12.51±0.73	23.42±1.93
120-PFD <sub>1</sub> PVA <sub>0</sub> L <sub>1</sub> -MeOH-0.5	5.08±0.11	10.92±0.13	19.38±0.11
130-PFD <sub>2</sub> PVA <sub>1</sub> L <sub>3</sub> -H <sub>2</sub> O-0.5	5.14±0.04	10.24±0.10	17.96±0.73
120-PFD <sub>2</sub> PVA <sub>1</sub> L <sub>3</sub> -H <sub>2</sub> O-0.5	4.91±0.15	9.45±0.23	16.41±0.33

Table 3: Characterization of API contents in sample particles by HPLC

Sample	Dilution multiple	Peak area	API theoretical content/%	API actual content/%	API relative content/%
130-PFD <sub>1</sub> PVA <sub>0</sub> L <sub>1</sub> -MeOH-0.5	1000	259631	50.0	36.2	72.4
120-PFD <sub>1</sub> PVA <sub>0</sub> L <sub>1</sub> -MeOH-0.5	100	3111507	50.0	40.8	81.6
130-PFD <sub>2</sub> PVA <sub>1</sub> L <sub>3</sub> -H <sub>2</sub> O-0.5	1000	249956	50.0	34.1	68.2
120-PFD <sub>2</sub> PVA <sub>1</sub> L <sub>3</sub> -H <sub>2</sub> O-0.5	100	3024046	50.0	40.7	81.4



Figure 2: The schematic diagram of scanning electron microscope

### 2.3.3 High Performance Liquid Chromatography (HPLC)

When the feed solution is atomized into droplets and dried into particles, the API in the particles may be lost for various reasons, resulting in the total mass of API in the final sample particles less than the theoretical mass. According to pirfenidone HPLC method, the content of pirfenidone in particles was determined by high performance liquid chromatograph (Shimadzu, Japan). A C18 (250 mm×4.6 mm, 5µm) column was used as the analytical column. Acetonitrile-water (containing 0.2% acetic acid) was 33: 67 as the mobile phase, the flow rate was 1.0 ml·min<sup>-1</sup>, the detection wavelength was set at 310 nm, the column temperature was 30 °C, and the sample size was 20 µl (Zhou 2017).

### 2.3.4 In Vitro Deposition Simulation

The deposition performance of particles in lung is mainly reflected by fine particle fraction (FPF) and mass median aerodynamic diameter (MMAD). The next generation impactor (NGI) was used to simulate lung deposition in vitro and to calculate FPF and MMAD. Figures 3 and 4 show the appearance and internal structure of NGI respectively. The samples were dispersed at a flow rate of 60 L/min and the pressure drop was set at 4 kPa. Each recipe will be dispersed for 4 s to achieve 4 L volume. The specific operation was carried out according to the weighing method specified in the British Pharmacopoeia. Data processing software CITDAS (Copley Science, Nottingham, UK) was used to calculate the FPF and MMAD of the sample.

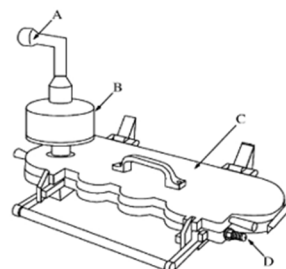


Figure 3: The appearance of next generation impactor, A: adapter-throat; B: pre-separator; C: NGI main body; D: air outlet

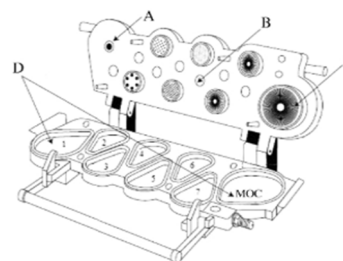


Figure 4: The internal structure of next generation impactor, A: primary jet hole; B: interstage channel; C: microporous collection; D: collecting stages

## 3. Results and discussion

### 3.1 Particle Size and Morphology

The sample particles were prepared according to the formulation and spray drying parameters in Table 1. Table 2 shows the size distribution of the above sample particles.

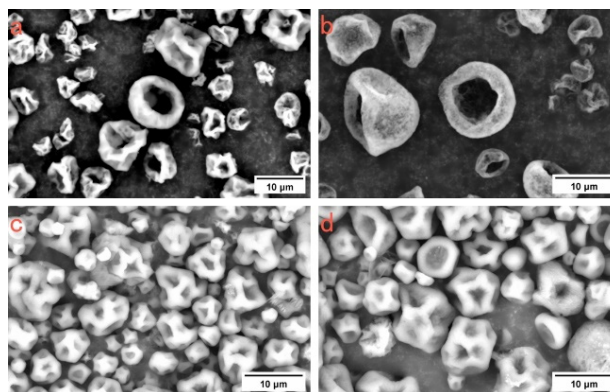


Figure 5: SEM images of (a) 130-PFD<sub>1</sub>PVA<sub>0</sub>L<sub>1</sub>-MeOH-0.5; (b) 120-PFD<sub>1</sub>PVA<sub>0</sub>L<sub>1</sub>-MeOH-0.5; (c) 130-PFD<sub>2</sub>PVA<sub>1</sub>L<sub>3</sub>- H<sub>2</sub>O-0.5; (d) 120-PFD<sub>2</sub>PVA<sub>1</sub>L<sub>3</sub>- H<sub>2</sub>O-0.5

Figure 5 showed the SEM images of sample particles. With the drying temperature of 130 °C and 120 °C, the particle morphology had little difference. It could be seen that after adding leucine to the precursor solution, all sample particles had wrinkled

outer surfaces due to the collapse of the hydrophobic shell formed by leucine on the surface of the droplet during the drying process. The particles prepared by direct dissolution of methanol were relatively loose. After adding polyvinyl alcohol, the particles had a higher degree of consolidation, and the particle size was slightly smaller than the former (120 °C, D50 from  $10.92 \pm 0.13 \mu\text{m}$  to  $9.45 \pm 0.23 \mu\text{m}$ ). However, due to the large molecular weight of polyvinyl alcohol, the particle density also increased. Therefore, increasing the leucine content in the two groups of sample particles with water as solvent made the surface wrinkles of the particles more obvious and denser, which was more conducive to improve their aerodynamic characteristics.

### 3.2 Characterization of API Content of Sample Particles by HPLC

The contents of API in the sample particles were characterized by HPLC (Table 3). The API theoretical content was the ratio of the theoretical mass of API in particles to the theoretical total mass of particles. The API actual content was the ratio of the actual mass of API in particles to the actual total mass of particles. The API relative content was the ratio of the API actual content to the API theoretical content.

When the inlet temperature of spray drying was 130 °C, the API actual contents in particles were low. When the solvents were MeOH and H<sub>2</sub>O respectively, the values were 36.2% and 34.1%, and the API relative contents were only 72.4% and 68.2%. However, when the temperature was reduced to 120 °C, the API actual contents were significantly increased, and the API relative contents were 81.6% and 81.4%. It could be found that the content of API in the sample particles was negatively correlated with the inlet temperature in the range of 130 to 120 °C. When the inlet temperature was 120 °C, the particles could have enough drug content. When delivering particles of the same mass, the inhalation efficiency of effective drugs for patients could be significantly improved.

The melting point of pirfenidone is 106-112 °C. In the process of high-temperature spray drying, the PFD temperature was lower than the actual inlet temperature due to the protection of wet bulb temperature in the early stage. However, when the inlet temperature was higher than the critical value, and PFD was gradually exposed to dry air with the evaporation of solvent, PFD may face high-temperature melting denaturation or glass transition. This may be the reason why the API content decreased when the inlet temperature was 130 °C, and improved when the temperature was reduced to 120 °C. Therefore, temperature protection in the drying process is one of the factors considered in the preparation of PFD dry powder particles.

### 3.3 In Vitro Deposition Properties

NGI was used to characterize the aerodynamic properties of sample particles and calculate their in vitro deposition (Figure 6). The MMAD of particles at the drying temperature of 120 °C was slightly less than that at 130 °C under the given proportion of each component in the sample, and the MMADs of 120-PFD<sub>1</sub>PVA<sub>0</sub>L<sub>1</sub>-MeOH-0.5 and 120-PFD<sub>2</sub>PVA<sub>1</sub>L<sub>3</sub>-H<sub>2</sub>O-0.5 were 4.871 μm and 5.688 μm respectively, and the PPFs were 27.814% and 26.168% respectively. In addition, the deposition of the latter in the last 6 stages (3,4,5,6,7, and MOC stages) was relatively high, which proved that the improvement of aerodynamic characteristics shown in the SEM image that caused by the ratio of polyvinyl alcohol and leucine made up the gap between the formulation and the organic solvent formulation. Eventually, considering the safety and technological advantages brought by water solvent, the formulation 120-PFD<sub>2</sub>PVA<sub>1</sub>L<sub>3</sub>-H<sub>2</sub>O-0.5 was selected for optimization.

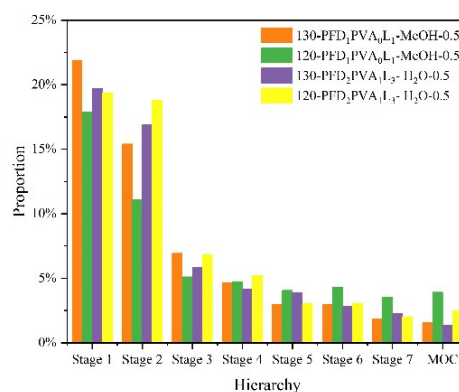


Figure 6: NGI results of sample particles for different formulations

## 4. Conclusions

In this study, a safe, stable and controllable pirfenidone dry powder particle was prepared by spray drying technology, and the structure-activity relationship between spray drying parameters and particle properties was explored through the adjustment of formulation and process. The core of this work was to replace the organic solvent with water in the preparation process of the precursor solution, and add the polymer polyvinyl alcohol for solubilization and slow-release effect and the leucine to improve aerodynamic characteristics. While avoiding the production explosion-proof requirements of organic solvents and the risk of solvent residues, the particle properties of finished products could still reach the approximate level under organic solvents, and had a high API content. The final improved formulation 120-PFD<sub>2</sub>PVA<sub>1</sub>L<sub>3</sub>-H<sub>2</sub>O-0.5 had a MMAD of 5.688 μm and a PPF of 26.168%. and its API relative content reached 81.4%.



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