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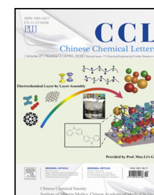

1
2 Original article

3 # Quantification of flupirtine maleate polymorphs using X-ray
4 powder diffraction

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A B S T R A C T

Flupirtine maleate, a pharmaceutical compound for treating psychotic disease in clinics, has seven polymorphs. Form A, with better crystal stability and bioavailability, has been widely used as the pharmaceutical crystal form. Unfortunately, it is usually found in a polymorphic mixture with form B. In this study, pure crystal forms of A and B were prepared and characterized by X-ray powder diffraction (XRPD), Fourier transform infrared spectroscopy (FT-IR) and thermal analysis. An XRPD–based method for the quantitative determination of the amount of the flupirtine maleate polymorphs form A and form B was also established through a systematic optimization of instrumental parameters. The results of the analytical methodology validation showed that the XPRD method had a broad quantitative range of 0–100% (w/w), good linear relationship, with $R^2 = 0.999$, excellent repeatability and precision and low limits of detection (LoD) of 0.15% (w/w) and quantification (LoQ) of 0.5% (w/w). The results also showed that the single-peak method was not as good as the whole pattern in reducing the influence of the preferred orientation, but this can be compensated for by a systematic optimization of instrumental parameters and validating the analytical methodology to reduce errors and obtain a good, repeatable, sensitive, and accurate method. This XRPD method can be used to analyze mixtures of flupirtine maleate polymorphs (forms A and B) quantitatively and control the quality of the bulk drug.
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9
10 ## 1. Introduction

11 Polymorphism creates challenges during drug development
12 and manufacturing because different polymorphs of a compound
13 have different physicochemical properties such as density,
14 morphology, solubility, dissolution rate, stability, and hygroscop-
15 icity. In addition, sometimes different polymorphs of the same
16 drug exhibit differences in bioavailability, efficacy, and drug
17 product performance in clinical situations. So the identification
18 and specification of polymorphs has become an important part of
19 the quality assurance process for pharmaceuticals [1]. In order to
20 control the polymorphic impurities of the final product, developing
21 an accurate quantification method for detecting low-level
22 polymorphic impurities in pharmaceuticals has become an
23 important aspect of drug development and manufacture.

24 Many analytical techniques, including infrared (mid- and near-
25 IR), FT-Raman, solid-state NMR spectroscopy, thermal methods,
26 and X-ray powder diffraction (XRPD) [2–7] have been used to
27 determine the polymorphic content of mixtures or the amorphous
28 content of crystalline materials. However, XRPD has become the
29 most preferred and extensively used technique for quantitatively
30 analyzing the purity of a polymorphic drug because of its
31 advantages, including the uniqueness of the X-ray powder patterns
32 of different compounds, non-destructive nature, simplicity, and the
33 ability to make the measurements of both the active ingredient and
34 the final commercial product at room temperature [8–14]. Single-
35 peak and whole pattern fitting are the primary quantification
36 methods of XRPD. The single-peak method is suitable for the
37 quantitative analysis of crystals due to its advantages, such as
38 requiring less information about the sample in advance, its simplicity,
39 and its high sensitivity. But this method relies heavily on having a
40 pure standard sample and is dependent on the orientation of the
41 crystal. Therefore, the single-peak method often requires validation
42 in practical applications. The whole pattern fitting method has a
43 higher signal to noise ratio (SNR), greater sensitivity, and a higher
44 level of specificity compared to the single-peak method, and it is not

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dependent on the purity of a standard sample, and the influence of the orientation is also reduced. However, the application of whole pattern fitting method is still limited by its requiring prior information about the sample's structure.

Flupirtine maleate (FPTM) (Fig. 1), 2-amino-3-carbethoxyamino-6-(4-fluorobenzylamino) pyridine maleate, an antipsychotic drug, has seven polymorphs. Forms A and B are the most common crystalline forms and usually coexist in a mixture [15]. Form A is the more stable anhydrous form at room temperature and is the one used as a medicine. Form B is unsuitable due to its metastability and is rapidly transformed into form A in concentrated isopropanol suspensions or at higher temperature [16]. Thus, it is necessary to develop a simple, highly sensitive and accurate technical method for quantifying the amount of form B in polymorphic (forms A and B) mixtures of flupirtine maleate. To the best of our knowledge, the crystal structures of forms A and B of FPTM have not been published. In this work, the single-peak-based XRPD method was utilized to quantify the polymorphic forms of FPTM (forms A and B). As mentioned before, an authentic and validated single-peak-based XRPD calibration curve requires an accurate identification and measurement of parameters, such as the intensity, height, and area of the diffraction lines, which is the most critical factor in developing any assay errors for solid-state forms. To reduce these errors, the instrument and sample preparation parameters, type of sample holders, sample rotation, particle size, and powder packing, all of which influence the quantification results by affecting the diffraction peak intensities, areas, and balance, must be considered [9,13,14].

This study focused on three objectives: i) characterizing the inherent nature of samples using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier transform infrared spectroscopy (FT-IR), and X-ray powder detection (XRPD) to test the purity and the choice of quantification methods; ii) optimizing the instrument and sample preparation parameters with the goal of minimizing the errors; and (iii) developing a quantification calibration curve, which has been validated and checked for assay errors, for quantifying the amount of form B in polymorphic of FPTM using data obtained by XRPD.

## 2. Experimental

### 2.1. Materials

FTPM form A and FTPM form B were prepared and supplied by the Hong de Pharmaceutical Co., Beijing and were used without any further purification. All other reagents and solvents obtained from commercial suppliers were used as received.

### 2.2. Instrumentation

Thermal analysis: DSC: A differential scanning calorimeter (DSC-Q2000; TA, UK) was used. The samples were heated from 40 to up to 200 °C at a heating rate of 10 °C·min$^{-1}$ under a nitrogen purge flow rate of 50 mL min$^{-1}$. The temperature end point was determined by the melting point of the less fusible component. The samples in all the DSC experiments weighed between 2.35 and 3.24 mg, with an accuracy of ±0.01 mg. TGA: The thermogravimetric measurements were performed using a Q500 TGA (TA, UK) system. The mass loss of the sample as a function of temperature was determined. 2.8590 mg of form A and 1.8480 mg of form B were weighed, respectively, with an accuracy of ±0.0001 mg, separately placed in an open alumina crucible, and then heated at a rate of 10 °C min$^{-1}$ under nitrogen purge (60 mL min$^{-1}$). And then a recorded TGA spectrum was obtained.

(FT-IR): The FT-IR spectra for each of the FTPM forms were obtained by averaging 32 scans performed using a Thermo Nicolet 6700 FT-IR spectrometer. About 2 mg of sample was gently ground with 200 mg of KBr and pressed into a 13 mm-diameter pellet with a hydraulic press at 700 MPa for 20 s. The spectrum for each sample was recorded over the 4000–400 cm$^{-1}$ spectral region at a resolution of 4 cm$^{-1}$.

XRPD: XRPD patterns for samples of different percentages of B/A were recorded at room temperature on a Bruker D8 Advance diffractometer (Karlsruhe, West Germany) that utilizes Cu K$\alpha$ radiation (1.54 Å) at 40 kV, 40 mA passing through a nickel filter with a 0.5° variable slit, a 2.5 mm solar slit, and a 1 mm receiving slit to obtain both reflection and transmission measurements. The diffractometer had a 2$\theta$ compensating slit and the accuracy of the peak positions was calibrated with $\alpha$-$Al_2O_3$ as standard sample. One hundred milligrams of the powder mixture was loaded into the 0.2 mm deep hollow of an aluminum sample holder equipped with a quartz monocrystal zero background plate. To ensure a flat surface that was continuous with the holder surface, a clean glass slide was used to compress the sample into the hollow of the holder plate. The samples were analyzed by a continuous mode X-ray powder diffraction analysis with a step size of 0.01° and a step time of 0.6 s over an angular range of 4–16°. During the measurements, the sample holder was rotated in the surface plane at 15 rpm. DIFFRAC$^{plus}$ EVA (ver. 9.0) diffraction software was used to analyze the resulting diffractograms.

## 3. Results and discussion

### 3.1. Solid-state characterization of crystal forms A and B

#### 3.1.1. Thermal analysis

The DSC curve (Fig. 2) for form A showed a melting endotherm at 164.88–168.37 °C, a subsequent recrystallization exotherm at 169.86–170.2 °C, and a final melt at 178.44–179.81 °C. Form B only had a single melting endotherm at 182.81–183.45 °C. The melting point and melting enthalpy are listed in Table 1.

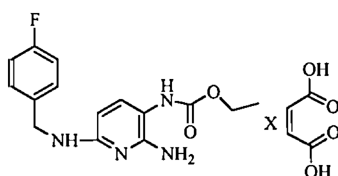

**Fig. 1.** Flupirtine maleate.

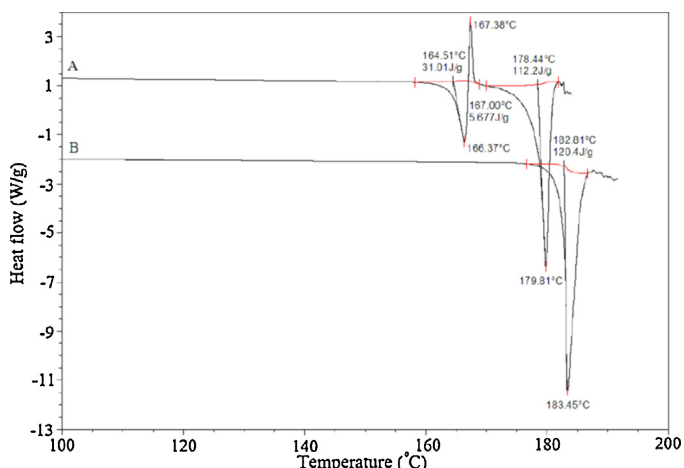

**Fig. 2.** DSC curves of forms A and B.

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