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STUDY ON ORAL ULCER POWDER USING TEMPERATURE-DEPENDENT X-RAY DIFFRACTION TECHNIQUE

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ABSTRACT

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The temperature-dependent XRD (TD-XRD) technique was used to rapidly detect the three main ingredients (*Indigo Naturals* (IN), borneol, and alum) of Oral Ulcer Powder (OUP) and impurities introduced in the process of manufacture of OUP. The results show that the three main ingredients of OUP can be monitored by XRD. The hexagonal $\text{Ca}(\text{OH})_2$, the rhombohedral CaCO_3 , and a small amount of SiO_2 survive in IN during the process called "Hit indigo with lime". The alum in OUP mainly consists of aluminum potassium sulfate ($\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$), with a small amount of ammonium alum ($\text{NH}_4\text{Al}(\text{SO}_4)_2$). The borneol in OUP gradually disappears with increasing T from 30 to 100°C , whereas, $\text{NH}_4\text{Al}(\text{SO}_4)_2$ and rhombohedral CaCO_3 survive in OUP. The TD-XRD technique can provide evidence of stability of pharmaceutical preparations and set up a rapid detection method for quality control of OUP.

KEYWORDS

Temperature-dependent X-ray diffraction, Chinese traditional patent medicines, Oral Ulcer Powder, quality control

1. INTRODUCTION

Chinese traditional patent medicines (CTPM) are widely used throughout the world because they have definite effect without side effects. The prescription of Oral Ulcer Powder (OUP) (Chinese name kouqiangkuiyangsan) is originally recorded in the *Pharmaceutical Standards of the Ministry of Health* [1]. OUP is composed of *Indigo Naturals* (IN), borneol, and alum, which have been used as heat-clearing and detoxifying, relieve pain and inflammation. Chromatography is generally adopted for quality control (QC) of indigo and indirubin in OUP [2-5]. However, the whole structural information of OUP has never been studied. OUP is a complex chemical system, which consists of dozens of independent, but mutually aggregated chemical constituents. If only one or more active components are used as quantitative and qualitative indicators, there is no method to reflect the overall quality of OUP.

New modern analytical methods are needed to be developed for QC of OUP. Fingerprint method has been widely regarded as a method to control the quality of CTPM. Although the composition of CTPM is complex, the XRD technique can effectively monitor the crystalline ingredients of some molecular crystals and inorganic excipients in CTPM and hence becomes an important means of QC of CTPM. XRD had been used to identify fingerprint of some Chinese herbs, analyses on several CTPMs, and QC of pharmaceutical excipients [6-8]. However, XRD still has some localization in QC of OUP because most plant herbs as initial materials have not crystalline structures.

In this work, with the help of International Centre for Diffraction Data (ICDD), the TD-XRD technique was used to study a typical CTPM OUP. From the point of view of material science, the temperature stability of OUP was evaluated, and the whole structural information of OUP was understood. The method of QC of OUP was explored.

2. EXPERIMENTAL

The information of oral ulcer powder (OUP), *Indigo Naturals*, borneol, and alum are listed in Table 1. These samples were crushed and ground in agate mortar for 20 min. The powders were screened with 100 mesh screen to prepare their fines, which were placed in an electronic moisture-proof cabinet for XRD measurements. The humidity in the cabinet was kept at 1 % and the storage temperature at 18°C .

Table 1: Information of Oral ulcer Powder and its ingredients

Item	Oral ulcer Powder	<i>Indigo Natural s</i>	Alum	borneol
Manufacturer	Beijing Tongrentang Pharmaceutical Group	Juxing <i>Indigo Natural s</i> Factory, Xianyou County, Fujian Province	Hebei Sirui Pharmaceutical Co., Ltd.	Sanjiu modern Chinese medicine co., Ltd.
Lot Number	151006	1601107	150801	
Collection Date	December 3, 2016	August 6, 2017	August 6, 2017	April 6, 2015

The fines of the above OUP and its ingredients were placed on a metal specimen stage in a sealing chamber. The temperature (T) detected by a thermocouple within the metal specimen stage can accurately reflect the temperature of the metal specimen stage owing to good heat conductivity of metal. Temperature drift error was $\Delta T < 1^\circ\text{C}$. After these fines were heated to a given T and kept for 30 min, powder XRD spectra were

measured from 25 to 100 °C using a DX-2700 X-ray diffractometer equipped with a LTK-450 meso-thermally controlled accessory (Dandong Haoyuan). At each T the XRD data was collected between $5^\circ \leq 2\theta \leq 70^\circ$ in steps of 0.02° .

3. RESULTS AND DISCUSSION

3.1 Room-Temperature XRD

The powder XRD patterns of OUP and three ingredients at room temperature are shown in Fig. 1. Each ingredient exhibits a series of characteristic peaks. The diffraction pattern of OUP is composed of multi-peaks of three ingredients IN, alum, and borneol. Vegetation-type IN shows a typical crystalline structure with high-intensity diffraction peaks (Figure 1(b)), which is consistent with partial peaks of OUP. Although alum is also a typical crystal (Figure 1(d)), the main peak at $2\theta = 31.92^\circ$ does not match any diffraction peak of OUP, indicating that this kind of alum is not a pharmaceutical excipient in this OUP, but rather ammonium alum ($\text{NH}_4\text{Al}(\text{SO}_4)_2$) with a hexagonal phase structure, as indicated by PDF 23-0001 (Figure 1(e)).

As a traditional Chinese medicine, borneol is a kind of crystallization that is obtained from the resin and volatile oil. Borneol molecules themselves have no XRD phenomenon, but they can form well-crystallized organic molecular crystals through intermolecular forces (van der Waals' forces or hydrogen bond). Borneol molecules can be arranged periodically along the three-dimensional space and therefore it shows a feature of strong XRD. Some diffraction peaks of OUP contain those of borneol, as denoted in Figure 1(a) [1]. Two XRD peaks at $2\theta = 13.28^\circ$ and 25.40° , which appear in the OUP, do not belong to these ingredients (Figure 1).

Figure 1: Room-temperature Powder XRD patterns of (a) OUP, (b) IN, (c) borneol, and (d) alum. (e) The simulated XRD pattern of ammonium alum (PDF 23-0001).

Figure 2: (a) Powder XRD pattern of Alum. The simulated XRD patterns of (b) ammonium alum (PDF 07-0022) and (c) aluminum potassium sulfate (PDF 07-0017).

The XRD spectrum of commercially available alum is shown in Fig. 2(a), in which the simulated XRD patterns of ammonium alum ($\text{NH}_4\text{Al}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$) (PDF 07-0022) and aluminum potassium sulfate ($\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$) (PDF 07-0017) are provided for comparison. Alum is a crystalline product of sulfate mineral alum [9]. The main composition of our alum sample is identified to be aluminum potassium sulfate. The existence of $2\theta = 14.92^\circ$ implies that a small amount of ammonium alum as impurities is mixed in our alum.

The powder XRD pattern of IN is shown in Fig. 3(a), in which the simulated XRD patterns of (b) calcium carbonate (PDF 47-1743) and (c) calcium hydroxide (PDF 76-0571) are provided for comparison. "Hit indigo with lime" is a necessary step in the production of IN. Except for the contained active components such as indigo and indirubin, IN also contained inorganic components such as lime and SiO_2 . Lime can be divided into calcium oxide (CaO) and slaked lime ($\text{Ca}(\text{OH})_2$). Addition of lime in IN can not only store carbon dioxide (CO_2) in soaking solution, but also react with CO_2 to transform into calcium carbonate (CaCO_3) [10, 11]. In order to determine the source of the diffraction peaks in IN, we simulated the XRD patterns of various $\text{Ca}(\text{OH})_2$ and CaCO_3 in ICDD. A series of XRD peaks of IN was identified to be composed of those of hexagonal $\text{Ca}(\text{OH})_2$ (PDF 76-0571), rhombohedral CaCO_3 (PDF 47-1743), and a small amount of SiO_2 , as shown in Figure 3.

Figure 3: Powder XRD patterns of (a) IN. The simulated XRD patterns of (b) calcium carbonate (PDF 47-1743) and (c) calcium hydroxide (PDF 76-0571).

3.2 Temperature-Dependent XRD

The TD-XRD patterns of OUP are shown in Figure 4. The intensity of the diffraction peaks lowers with increasing T from 30 to 100°C. The XRD peaks of borneol completely disappears at $T = 100^\circ\text{C}$, revealing that it is easy to sublimate borneol as the temperature is increased [12,13]. Some diffraction peaks survive at $T = 100^\circ\text{C}$. Two peaks at $2\theta = 10.54^\circ$ and 24.02° arise from $\text{NH}_4\text{Al}(\text{SO}_4)_2$ and a peak at $2\theta = 29.34^\circ$ from rhombohedral CaCO_3 in IN.

Figure 4: Temperature-dependent XRD patterns of OUP

4. CONCLUSIONS

The temperature-dependent XRD technique was used to study a typical Chinese traditional patent medicine — Oral Ulcer Powder (OUP) fabricated by the three ingredients: *Indigo Naturals*, alum, and borneol.

(1) The XRD peaks of *Indigo Naturals* are identified to arise from hexagonal $\text{Ca}(\text{OH})_2$, rhombohedral CaCO_3 and a small amount of SiO_2 . These three impurities are mixed in *Indigo Naturals* during the process called “Hit indigo with lime”.

(2) The XRD spectrum of OUP is composed of those of *Indigo Naturals*, borneol, and ammonium alum.

(3) Alum in OUP is different with commercially available alum. The latter mainly consists of aluminum potassium sulfate, with a small amount of ammonium alum.

(4) The borneol in OUP gradually disappears with increasing T from 30 to 100°C, revealing its sublimation nature. Whereas, $\text{NH}_4\text{Al}(\text{SO}_4)_2$ and rhombohedral CaCO_3 survive in OUP.

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