The Method Development and Validation of Powder X-ray Diffraction for the Identification of Counterfeit Pharmaceuticals

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Abstract

Counterfeit pharmaceuticals are illegally manufactured and widely distributed throughout the world, which presents a major threat to public health. Counterfeit pharmaceuticals are unapproved and unregulated products which may contain dangerous or harmful ingredients or an insufficient amount of the active pharmaceutical ingredient (API) patients require to stabilize or improve their health.[1] Therefore, the FDA's Forensic Chemistry Center is always looking for fast, easy to use and reliable instrumental techniques to screen and identify a suspected counterfeit product from an authentic product ensuring that the legal supply chain is secure and maintaining the safety of the public health.[2]

X-Ray Powder Diffraction (XRD) has been shown to be a useful technique in the analysis of suspect counterfeit pharmaceutical products.[3] This poster describes the development method for analyzing pharmaceutical solid dosage forms, APIs and excipients using the Bruker AXS D2 Phaser diffractometer (XRD) instrument at the Food and Drug Administration's Forensic Chemistry Center (FCC). The method was validated by measuring the XRD patterns of known counterfeit pharmaceutical products and comparing them to the XRD patterns of authentic products.

Introduction

Counterfeit pharmaceuticals are illegally manufactured products and are widely distributed throughout the world, which is a major public health threat.[5,6,12] These unregulated products may contain the incorrect API, may not contain any API, or may contain the correct API at the incorrect dosage strength.[1,12] Counterfeits have been found in brand and generic names of pharmaceuticals, and have been discovered in both developing and developed countries. [7,8] It has been observed that some therapeutic groups of pharmaceuticals may be more likely to be counterfeited than others, such as antibiotics, antihistamines, anti-malarials, hormones, steroids and other therapeutic products. As a results from these counterfeit products many patients will experience prolonged illnesses, exacerbated symptoms or even death. [9]

Various techniques have been developed to screen and identify counterfeit pharmaceuticals. X-Ray Powder Diffraction (XRD) is a fast, reliable and easy to use technique often used in forensic science to analyze various types of trace evidence, such as paint and illegal drugs. [10] It has been found that most material have a distinct XRD pattern and can be identified within a compound or mixture when compared to database of a known XRD pattern.

X-ray powder diffractometers consist of several different parts including the cathode ray tube, sample holder, and detector.[7,10,11] The cathode ray tube produces x-rays by heating a metal filament, a voltage is then applied to the tube causing the x-rays to accelerate toward the crystalline material at a given angle θ.[7,11] The incident beam is diffracted by multiple layers of atoms of the material creating constructive or destructive interference of the x-ray beams returning to the detector at an angle of 2θ from the incident beam. For the detector to produce an XRD peak, the diffracted beams must have diffraction rays that possess constructive interference, which is only produced when the beams fit the criteria of Bragg's Law, sin θ = nλ/2d.

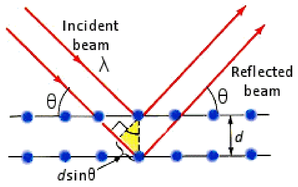

Figure 1. Diagram of Powder X-ray diffraction[4]

Materials and Methods

Materials used for this experiment:

- Bruker D2 Phaser desktop X-ray diffractometer
- Various bulk powder excipients
- Bulk powder active pharmaceutical ingredients
- Known authentic dosage forms of various pharmacuticals
- Known counterfeit dosage forms of various pharmaceuticals
- Carver Pellet press
- Crescent Wig-L-Bug
- Mortar Pestle
- Common laboratory equipment: spatula, balance, etc.

Method development for this study:

Various Method for Sample Preparation:

1. Various amounts of acetylsalicylic acid, 10mg, 30mg, 40mg were ground with mortar and pestle then compressed into the PMMA sample holder.
2. Various amounts of acetylsalicylic acid, 20mg, 40mg, 60mg, were ground with mortar and pestle then compressed into a Carver pellet.
3. Various amounts of acetylsalicylic acid, 20mg, 40mg, 60mg, were ground with Wig-L-Bug and compressed into a Carver pellet.

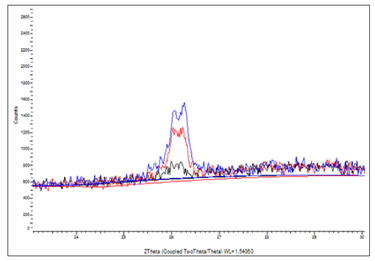

Figure 2. Acetylsalicylic acid ground with a mortar and pestle, then pressed into the PMMA sample holder.

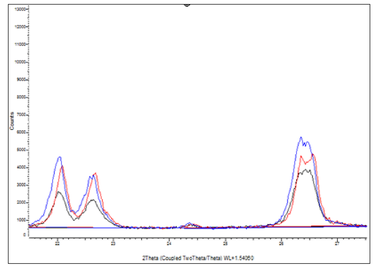

Figure 3. Acetylsalicylic acid ground with a mortar and pestle, then pelleted with a Carver Press.

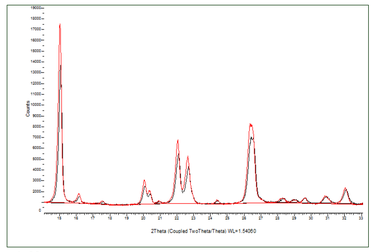

Figure 4. 60mg acetylsalicylic acid ground with the mortar and pestle and then pelleted (red). 60 mg acetylsalicylic acid ground with the Wig-L-Bug and then pelleted. (black)

Results

Variability Studies between Authentic Dosage Forms

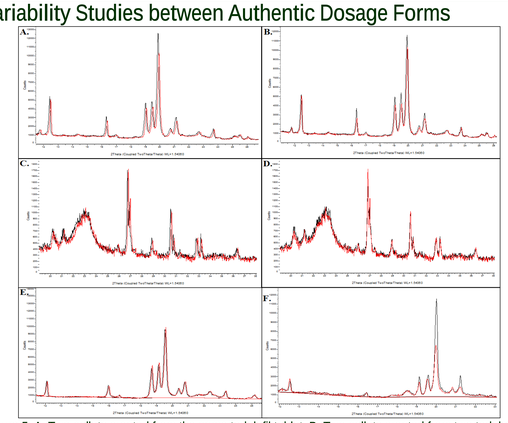

Figure 5. A. Two pellets created from the same tadalafil tablet. B. Two pellets created from two tadalafil tablets. C. Two pellets created from the same sildenafil tablet. D. Two pellets created from two sildenafil tablets. E. Aripiprazole patterns of two lot numbers, Lot # 918196 in red and Lot # 406824 in black. F. Atrazanavir patterns of two lot numbers, Lot # 722027 in red and Lot # 897823 in black.

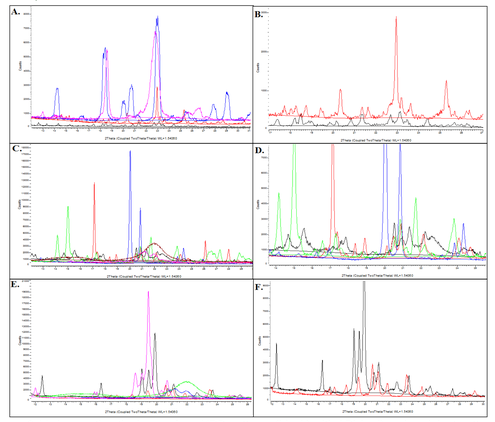

Figure 6. Various authentic dosage form XRD patterns (black) with API (red) and excipient patterns (various colors) overlain on the left. The authentic dosage form pattern and API standard pattern overlain on the right. A & B. Clopidogrel. C&D. Abacavir. E&F. Olanzapine 20mg.

Comparison of Authentic and Counterfeit Dosage Forms

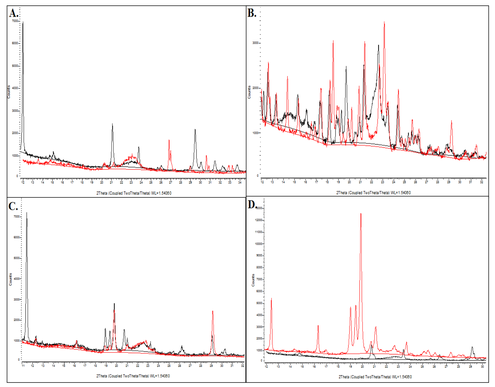

Figure 7. Patterns of counterfeit and authentic pharmaceutical products. A. Counterfeit and authentic sildenafil 100mg. B Counterfeit and authentic clopidogrel 75mg. C. Counterfeit and authentic atorvastatin 20mg. D. Counterfeit and authentic tadalafil 20mg. Counterfeit = Black; Authentic = Red

Conclusions

In conclusion, a method was developed to analyze and produce quality XRD patterns of pharmaceutical products, authentic, suspect, or counterfeit, using the Bruker D2 Phaser x-ray powder diffractometer. The best method preparation for analysis was to use the Wig-L-Bug device to finely ground the powder and the Carver press to create a pellet. It was found that authentic dosage form products result in the same overall XRD patterns between tablets and lot numbers, with the exception of peak shifts less than 0.2º. Peak shifting of less than 0.2° is a normal occurrence when analyzing powder material, the shift is due to the random orientations of the crystalline material during the packing process, each sample will possess different crystalline orientations.[11]

The method was validated with the use of information found in USP general chapter <941> stating that if peak shifts within a suspect product XRD pattern are greater than 0.2º for a given 2θ-diffraction angle compared to the authentic XRD pattern, then the product meets the criteria for a counterfeit product. Counterfeit pharmaceuticals can also be distinguished from authentic pharmaceuticals by examining the overall XRD patterns. Counterfeit product patterns will contain missing peaks, additional peaks and peak shifts. This method and validation will allow the Forensic Chemistry Center to use the diffractometer as an additional technique to distinguish counterfeit pharmaceuticals from authentic pharmaceuticals.

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