Indonesian Journal of Chemistry and Environment
Vol. 7, No. 2, December 2024, pp. 93~103
e-ISSN: 2599-3186

Applications and Future Potential of X-ray Diffraction in Pharmaceutical Polymorphism: A Literature Review

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Article Info

Article history:

Received Nov 13th, 2024
Revised Nov 29th, 2024
Accepted Dec 2nd, 2024

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ABSTRACT

Polymorphism in drug compounds is a significant phenomenon in pharmacy because it affects physicochemical properties such as solubility, stability, and bioavailability, which impact the effectiveness and safety of drugs. X-ray diffraction (XRD) is one of the methods that can be used to identify and analyze the polymorphic properties of drug compounds. This article reviews the utilization of XRD in various studies, showing that this method is effective for identifying polymorphism, detecting changes in crystal forms, monitoring crystalline phase transitions, and characterizing the formation of new crystalline phases. Although very useful, XRD has limitations in detecting amorphous phases and requires optimal sample preparation. For more comprehensive results, XRD is often combined with other techniques such as DSC and FTIR. Overall, XRD plays an important role in drug development and quality control, and this technology is expected to continue evolving, including its ability to directly monitor the crystallization process to enhance drug quality and stability.

***Keyword*:** X-Ray Diffraction, XRD, Polymorphism, Crystal, Method

1. INTRODUCTION

In pharmaceutical, a deep understanding of the polymorphic properties of drug compounds is essential. Polymorphism is a phenomenon where a compound can exist in two or more distinct crystal forms, known as polymorphs. In a pharmaceutical context, polymorphism influences the physicochemical properties of drugs, including solubility, stability, and bioavailability (Tantia et al., 2024). Variations in crystal forms can impact how a drug is absorbed and metabolized in the body, which in turn, can affect its therapeutic effectiveness and safety (Queljoe et al., 2015).

The identification and characterization of polymorphism are crucial aspects of drug development, as polymorphism can influence the physicochemical properties of drug compounds. Studies show that over 50% of drug compounds have the ability to form more than one crystal form, each with potentially different properties, such as solubility, stability, and bioavailability (Ainurofiq et al., 2020). For example, differences in crystal structure can lead to significant variations in the dissolution rate and stability of a drug, which can in turn, impact the therapeutic effectiveness and safety of pharmaceutical products (Surov et al., 2023).

In drug formulation development, polymorphism is also an important factor. The use of nanotechnology in drug development can enhance formulation effectiveness by leveraging the polymorphic properties of compounds (Tantia et al., 2024).

One of the most effective analytical methods for studying the crystal structure of compounds is X-ray diffraction (XRD). X-ray diffraction (XRD) is a highly important analytical technique in materials science and physics, used to determine the crystal structure of various materials (Purawiardi, 2021). The basic principle of X-ray diffraction is rooted in the interaction between X-rays and the atoms in a crystal. When X-rays strike a crystalline material, the electromagnetic waves are reflected by the atomic layers in the crystal. This process produces a diffraction pattern that can be analyzed to obtain information about interatomic spacing, crystal orientation, and crystal grain size (Didik, 2020).

An important aspect of X-ray diffraction analysis is Bragg's law, which states that diffraction occurs when the X-ray wavelength is proportional to the interplanar spacing of atoms in the crystal. This law can be expressed by the equation: $n\lambda = 2d \sin \theta$, where *n* is an integer, *λ* is the X-ray wavelength, *d* is the interlayer spacing, and *θ* is the diffraction angle (Didik, 2020). By using this technique, researchers can determine crystal structure parameters, such as grain size and lattice strain, which are essential in the development of new materials (Purawiardi, 2021; Purawiardi & Astawa, 2022).

In its applications, X-ray diffraction has been widely used for the characterization of various materials, including nanoparticles and complex compounds. For example, research by Purawiardi and Astawa demonstrated that diffraction peak broadening can be used to evaluate lattice strain effects on metallic materials, providing deeper insights into the mechanical properties of these materials (Purawiardi, 2021; Purawiardi & Astawa, 2022).

XRD is one of the most effective analytical methods for studying the crystal structure of pharmaceutical compounds. XRD can provide detailed information on crystal structure, including particle size, shape, and crystal orientation, all of which contribute to polymorphism characterization (Rajamma et al., 2015). Therefore, XRD not only serves as a tool for identifying polymorphs but also as an important method in drug development and quality control (Rajamma et al., 2015).

The main objective of this article is to review the use of XRD in the field of pharmaceuticals and drug compounds through a literature review and evaluate the limitations of this method.

2. RESEARCH METHOD

The method used in this study is a literature review of 15 journal researches. Literature searches were conducted through the online database Google Scholar. The main keywords used were "Difraksi Sinar-X," "XRD," "Polimorfisme," "Kristal," "X-Ray Diffraction," "Polymorphism," and "Crystal."

The inclusion criteria for this study include journals published between 2014 and 2024, that use XRD to analyze drug compounds, and studies focusing on polymorphism and crystal structure. Meanwhile, the exclusion criteria include studies that do not use XRD, focus on non-drug compounds, and articles outside the specified timeframe.

3. RESULTS AND ANALYSIS

The results of the literature review conducted will be presented in Table 1, which showcases various applications of X-ray diffraction methods in pharmacy.

Table 1. The Use of X-ray Diffraction Method in Pharmacy

No.	Title	Sample	The Use of XRD	Reference
1.	Five Novel Polymorphs of Cardarine GW501516 and Their Characterization by X-ray Diffraction, Computational Methods, Thermal Analysis and a Pharmaceutical Perspective	GW501516 (Cardarine)	Identification of polymorphism	(Turza et al., 2024)
2.	Irbesartan desmotropes Solid-state characterization,	Irbesartan	Identification of polymorphism	(Araya-Sibaja et al., 2019)

No.	Title	Sample	The Use of XRD	Reference
	thermodynamic study and dissolution properties			
3.	Karakterisasi dispersi padat meloksikam dengan matriks campuran PEG 6000 dan poloxamer 188 yang dibuat menggunakan metode kombinasi	Solid dispersion of meloxicam with a mixed matrix of PEG 6000 and poloxamer 188.	Characterization of polymorphic changes	(Najih et al., 2021)
4.	Karakterisasi Sifat Fisikokimia Dispersi Padat Celecoxib–PEG 4000 dengan Perbandingan Tiga Formula menggunakan Metode Co-grinding	Celecoxib–PEG 4000	Characterization of polymorphic changes	(Fadhila et al., 2022)
5.	Kokristalisasi Aspirin Dan Asam Tartrat Dengan Metode Penguapan Pelarut	Standard aspirin and aspirin-tartaric acid	Detection of new crystalline phase formation	(Aini et al., 2021)
6.	Pembentukan dan Karakterisasi Fisika Kimia Ko-Kristal Piroxicam-Asam Tartrat-Sakarin dengan Metode Solvent Drop Grinding	Piroxicam-tartaric acid-saccharin cocrystal	Detection of new crystalline phase formation	(Imanto et al., 2023)
7.	Pengaruh HPMC dan PVP K-30 Sebagai Stabilizer Pada Nanopartikel Telmisartan Terhadap Sifat Fisikokimia dan Laju Disolusi	Telmisartan-HPMC-PVP K-30	Identification of polymorphism	(Makmur et al., 2023)
8.	Pengembangan Sistem Dispersi Padat Ezetimibe dengan Matriks PEG 8000 menggunakan Metode Peleburan	Ezetimibe, solid dispersion of ezetimibe - PEG 8000, and surface adsorption solid dispersion	Characterization of polymorphic changes	(Rahayyu et al., 2024)
9.	Enhanced Dissolution Rate of Ketoprofen by Co-grinding Technique with Hydroxypropyl Methylcellulose E6 polymer	Ketoprofen, HPMC E6, physical mixture of ketoprofen–HPMC E6, and solid dispersion of ketoprofen–HPMC E6 with various ratios	Characterization of polymorphic changes	(Hilaliyati et al., 2017)
10.	Polymorphism of Carbamazepine Pharmaceutical Cocrystal: Structural Analysis and Solubility Performance	Carbamazepin : methylparaben (1:1) dan (1:0,25)	Identification of polymorphism	(Surov et al., 2023)
11.	Structural Characterization of Co-Crystals of Chlordiazepoxide with p-Aminobenzoic Acid and Lorazepam with Nicotinamide by DSC, X-ray Di raction, FTIR and Raman Spectroscopy	Chlordiazepoxide-p-Aminobenzoic Acid cocrystal and Lorazepam-b Nicotinamide cocrystal	Detection of new crystalline phase formation	(Garbacz et al., 2020)
12.	Synthesis and Characterization of a (−)-Epicatechin and Barbituric Acid Cocrystal Single-Crystal X-ray Diffraction and	(−)-Epicatechin and barbituric acid cocrystal.	Detection of new crystalline phase formation	(Budziak-Wieczorek & Maciołek, 2021)

No.	Title	Sample	The Use of XRD	Reference
	Vibrational Spectroscopic Studies			
13.	Synthesis and Structure Characterization of Three Pharmaceutical Compounds Based on Tinidazole	Three new pharmaceutical compounds based on tinidazole and common benzoic acid.	Identification of polymorphism	(Li et al., 2023)
14.	Novel Polymorph of Favipiravir—An Antiviral Medication	Favipiravir recrystallized from ethyl acetate	Monitoring of polymorphic phase transformation	(Goloveshkin et al., 2021)
15.	Thermal characterization, polymorphism, and stability evaluation of Se-NSAID derivatives with potent anticancer activity	Selenium derivative NSAIDs (Se-NSAID)	Identification of polymorphism	(Ramos-Inza et al., 2024)

Based on the analysis of 15 journals presented in the table, the X-ray diffraction method has proven to be effective in various aspects of pharmaceutical polymorphism analysis. The use of this method enables the identification of polymorphism. Additionally, X-ray diffraction is used in the characterization of polymorphic changes, detecting the formation of new crystalline phases, and monitoring polymorphic phase transformations.

3.1. Identification of Polymorphism

Polymorphism in pharmaceutical compounds is a phenomenon where a substance can exist in more than one different crystal form, known as a polymorph. This phenomenon is crucial in drug development and formulation because it can affect the physicochemical properties, including solubility, stability, and bioavailability of pharmaceutical active compounds (Santos et al., 2014). Polymorphism can lead to variations in therapeutic efficacy and drug safety, making a deep understanding of polymorphism essential in the pharmaceutical industry (Santos et al., 2014).

Polymorphism identification is a crucial step in the characterization of pharmaceutical compounds because variations in crystal structure can have a significant impact on various physicochemical properties, stability, and bioavailability of the compound (Turza et al., 2024). Polymorphism affects the interaction of a compound with its biological environment and, ultimately, can determine the compound's effectiveness in clinical applications (Turza et al., 2024). Several studies have employed X-ray diffraction techniques to determine the presence of polymorphism in certain compounds and identify the crystal forms formed by each polymorph (Turza et al., 2024). For example, in a study on the compound GW501516, X-ray diffraction, both on single crystals and powdered samples, was used to characterize five new polymorphs (Turza et al., 2024). The results of this study indicated that each polymorph had a different molecular configuration and intermolecular interaction, which in turn could affect the stability, solubility, and thermal properties of the compound (Turza et al., 2024). In the study of the compound Cardarine (GW501516), five new polymorphs were successfully identified and analyzed using X-ray diffraction. The following is a summary of the characteristics of each polymorph.

- GW-1: This polymorph is the initial form obtained through recrystallization in acetonitrile. GW-1 has a monoclinic crystal system with symmetry space P21/c.
- GW-2: This form is obtained from a mixture of pentane and acetone, and it also crystallizes in a monoclinic system but with symmetry space P21/n.
- GW-3: This polymorph is crystallized in isopropyl alcohol and has a monoclinic crystal system with symmetry space C2/c. Although similar to GW-1, its main difference is the rotation of the central heterocyclic ring.

- GW-4: Found as a minor form in the initial sample, GW-4 has an orthorhombic crystal system with symmetry space Pca21.
- GW-5: This polymorph is obtained through recrystallization in methyl isobutyl ketone, but the resulting crystals are of low quality, so the final structure was determined using powder X-ray diffraction techniques. GW-5 crystallizes in a triclinic system with symmetry space P-1 and shows high flexibility in the methylsulfonyl group. This polymorph also has small cavities in its structure, allowing for the storage of residual solvent.

In another study involving the compound irbesartan, powder X-ray diffraction (PXRD) successfully identified two desotropic forms, namely form A and form B, each with a unique and distinct diffraction pattern (Araya-Sibaja et al., 2019). In this case, form A was found to have higher solubility and good stability at room temperature, while form B proved to be more susceptible to degradation under high humidity conditions and elevated temperatures (Araya-Sibaja et al., 2019).

In a study involving carbamazepine (CBZ) cocrystals with methylparaben (MePRB), the use of X-ray diffraction, both on single crystals and high-resolution powder, allowed for the identification of two polymorphic forms, referred to as form I and form II (Surov et al., 2023). Although both polymorphic forms exhibit similarities in hydrogen bonding and molecular arrangement, form II demonstrates higher thermodynamic stability compared to form I, as well as better dissolution performance, making it a more promising candidate for pharmaceutical formulation development (Surov et al., 2023). Additionally, X-ray diffraction was also applied to identify polymorphism in three tinidazole-based compounds, where unique hydrogen bonding patterns were found in each formed crystal structure, indicating that this polymorphism contributes to the enhanced thermal stability of the tinidazole compounds compared to their base components (Surov et al., 2023).

In the study by Li et al. (2023), X-ray diffraction (XRD) was used to identify the structure and polymorphism of three tinidazole-based compounds created through slow solvent crystallization techniques. Each compound was characterized using XRD on single crystals to identify its crystal structure in detail, which then provided information about hydrogen bonding and other supramolecular interactions (Li et al., 2023).

- Compound 1: Tinidazole combined with 2,6-dihydroxybenzoic acid (2,6-DHBA) forms a monoclinic crystal structure.
- Compound 2: Tinidazole with 4-methylsalicylic acid (4-MAC) produces crystals in a triclinic system.
- Compound 3: The combination of tinidazole with 5-chloro-2-hydroxybenzoic acid (5-C-2-HBA) results in another triclinic crystal structure, where XRD identified the presence of a tetramer formed from hydrogen bonding between hydroxyl and carboxyl groups.

The XRD results indicate that the three compounds possess distinctive hydrogen bond configurations, which enhance thermal and structural stability compared to pure tinidazole or carboxylic acid (Li et al., 2023). Each polymorph exhibits greater rigidity and thermal stability, making each structure a more stable candidate for pharmaceutical formulation (Li et al., 2023).

The last one, in a study on selenium-containing NSAID derivatives (Se-NSAIDs), X-ray diffraction was used to identify two polymorphic forms of a naproxen derivative and an indomethacin derivative (Ramos-Inza et al., 2024). These forms showed differences in crystal structure, particularly before and after heating and subsequent cooling (Ramos-Inza et al., 2024), although both polymorphic forms demonstrated similar cytotoxic potential against the cancer cells tested (Ramos-Inza et al., 2024).

The use of X-ray diffraction on these various compounds demonstrates how polymorphism identification can provide essential insights into a compound's stability, solubility, and pharmaceutical performance, which are key considerations in the optimal drug development process. Based on these studies, X-ray diffraction has proven to be an effective tool for identifying and characterizing pharmaceutical compounds by observing their polymorphic patterns.

3.2. Characterization of Polymorphic Changes

X-ray diffraction (X-Ray Powder Diffraction or XRPD) was used to characterize polymorphic changes in meloxicam solid dispersions (Najih et al., 2021). The use of XRPD aimed to observe the crystallinity pattern of meloxicam in a PEG 6000 and Poloxamer 188 matrix (Najih et al., 2021). Test results showed that the diffractogram of meloxicam solid dispersion at ratios of 99:1 and 98:2 displayed a decrease in intensity and peak sharpness at specific angles, namely 13.5°, 15.0°, and 18.5° (Najih et al., 2021). This reduction in peak intensity indicates a decrease in crystallinity, suggesting a transition from a crystalline to an amorphous form (Najih et al., 2021). This reduction in crystallinity is expected to enhance the dissolution rate of meloxicam, ultimately helping to improve its bioavailability (Najih et al., 2021).

Additionally, X-ray diffraction (X-Ray Diffraction or XRD) was also used to analyze polymorphic changes in celecoxib within a solid dispersion system created through the co-grinding method (Fadhila et al., 2022). The primary goal of XRD was to determine whether celecoxib retained its crystalline form or transformed into an amorphous form after processing and mixing with the PEG 4000 polymer (Fadhila et al., 2022). XRD analysis results showed a decrease in the crystalline peak intensity of celecoxib in the solid dispersion compared to pure celecoxib and the physical mixture (Fadhila et al., 2022). In pure celecoxib, sharp crystalline interference peaks were observed, while in the solid dispersion formula, these peak intensities gradually decreased (Fadhila et al., 2022). This indicates that most of the celecoxib transitioned from a crystalline to an amorphous form (Fadhila et al., 2022). This change helps improve the solubility and dissolution rate of celecoxib, as the amorphous form is generally more soluble than the crystalline form (Fadhila et al., 2022).

In the study by Makmur et al. (2023), XRD was performed to compare the diffraction patterns of pure telmisartan, a physical mixture of telmisartan with stabilizers, and telmisartan nanoparticles in two different formulas (Makmur et al., 2023). XRD results showed that pure telmisartan produced sharp crystalline peaks at certain 2θ angles, reflecting a high degree of crystallinity (Makmur et al., 2023). However, after the nanoparticle preparation process with HPMC and PVP K-30, the intensity of these crystalline peaks significantly decreased without the appearance of new peaks, indicating a partial transition to an amorphous phase without the formation of a new crystal phase (Makmur et al., 2023). This decrease in intensity indicates a reduction in crystallinity, suggesting a shift in molecular structure towards an amorphous form (Makmur et al., 2023). The polymorphic characterization by XRD in this study showed that stabilizing telmisartan with HPMC and PVP K-30 effectively reduced crystallinity and created a partially amorphous phase, which is expected to improve the dissolution and bioavailability of the compound (Makmur et al., 2023). The absence of new peaks in the XRD pattern of the nanoparticles indicates that the changes that occurred were limited to crystallinity modification, not the formation of a new crystal phase or transformation to another polymorph (Makmur et al., 2023).

Similarly, in the study by Hilaliyati et al. (2017), X-ray Diffraction (XRD) was used to characterize polymorphic changes in ketoprofen that had been milled with HPMC E6, a hydrophilic polymer. The purpose of using XRD in characterizing polymorphic changes was to observe alterations in crystallinity that could affect the physicochemical properties of the material, such as solubility and dissolution rate. XRD works by producing diffraction patterns that reflect the atomic or molecular arrangement within a crystal structure. In pure ketoprofen, X-ray diffraction showed sharp peaks at specific 2θ angles, indicating a high degree of crystallinity (Hilaliyati et al., 2017). After ketoprofen was milled with HPMC E6, the XRD results showed a decrease in crystalline peak intensity, indicating a reduction in crystallinity and an increase in amorphousness. This amorphization process was marked by the weakening or disappearance of some diffraction peaks in the XRD pattern, leading to a more amorphous structure. As the amount of HPMC E6 increased, the diffraction peak intensity further decreased, indicating that ketoprofen's crystalline structure had transformed into a more dominant amorphous form. This amorphization is expected to enhance the dissolution rate of ketoprofen, as the amorphous structure has higher free energy than the crystalline structure, allowing its molecules to more readily dissolve into solution (Hilaliyati et al., 2017). The results of polymorphic characterization of ketoprofen milled with HPMC E6 showed a significant reduction in ketoprofen's crystallinity, indicating a shift towards an amorphous phase. This

reduction was identified by the decreased intensity of crystalline peaks in the XRD pattern of ketoprofen after milling. In the formula with a ketoprofen: HPMC E6 ratio of 1:2, the crystalline peak intensity of ketoprofen was the lowest compared to other formulas, indicating that the higher the amount of HPMC E6, the greater the degree of amorphization achieved (Hilaliyati et al., 2017).

X-ray diffraction (XRD) analysis also plays a crucial role in identifying and evaluating the changes in the crystalline structure of ezetimibe after being formulated into a solid dispersion system with PEG 8000 (Rahayyu et al., 2024). In its pure form, ezetimibe exhibits strong crystalline characteristics, indicated by three main diffraction peaks at 2θ angles of 7.78º, 15.70º, and 21.73º (Rahayyu et al., 2024). These angles represent the positions where X-ray diffraction reaches the highest intensity, making them useful reference points for identifying the presence and degree of crystallinity in the material (Rahayyu et al., 2024). These peaks show that the ezetimibe molecules are arranged in a regular crystalline pattern, resulting in sharp and intense diffraction peaks in its diffractogram (Rahayyu et al., 2024). After the formation of the ezetimibe solid dispersion with PEG 8000, the diffraction peaks at these angles experienced a significant reduction in intensity (Rahayyu et al., 2024). This decrease indicates a reduction in the crystallinity of ezetimibe in the mixture (Rahayyu et al., 2024). When ezetimibe is mixed with PEG 8000 through a melting process, PEG 8000 acts as a carrier or matrix that dissolves the ezetimibe molecules into a more disordered form, thereby inhibiting the formation of a stable crystalline structure (Rahayyu et al., 2024). As the amount of PEG 8000 in the system increases, the intensity of the diffraction peaks at 7.78º, 15.70º, and 21.73º continues to decrease, indicating that more ezetimibe molecules are in an amorphous state (Rahayyu et al., 2024). This transformation from crystalline to amorphous form is important because amorphous forms typically have higher free energy than crystalline forms (Rahayyu et al., 2024). Therefore, the amorphous form tends to be more reactive and has higher solubility because its disordered arrangement makes the molecules more easily released into solution (Maulidia Rahayyu et al., 2024).

3.3. Detecting The Formation of New Crystalline Phases

X-ray diffraction (XRD) plays a crucial role in detecting the formation of new crystalline phases, especially during the co-crystallization process, where changes in the crystal structure can affect the physicochemical properties of a compound. For example, in the study by Imanto et al. (2023), XRD was used to analyze the structural changes of piroxicam after co-crystallization with tartaric acid and saccharin. The XRD results showed a decrease in intensity at several diffraction peaks, indicating the formation of a new crystalline phase. This decrease in intensity suggests changes in the crystal structure of piroxicam that may affect its solubility and other physicochemical properties (Imanto et al., 2023). XRD was also applied in the research by Garbacz et al. (2020), who used PXRD techniques to detect the formation of a new crystalline phase in lorazepam co-crystals with nicotinamide. The PXRD analysis revealed the emergence of new diffraction peaks that were not present in the initial physical mixture, confirming the formation of a new, more stable crystalline phase. The formation of this new crystalline phase has the potential to influence the pharmacological properties of the drug (Garbacz et al., 2020).

Similarly, in the study by Budziak-Wieczorek & Maciołek (2021), XRD was used to detect the formation of a new crystalline phase in the co-crystal of (−)-epicatechin (EC) with barbituric acid (BTA). PXRD revealed unique diffraction peaks that were not found in the pure components, confirming the formation of a new, stable crystalline phase through strong hydrogen bonding interactions between EC and BTA (Budziak-Wieczorek & Maciołek, 2021). In contrast, in the study by Aini et al. (2021) on the co-crystallization between aspirin (ASP) and tartaric acid, although there were changes in peak intensity, no new peaks were found that would indicate the formation of a new crystalline phase (Aini et al., 2021).

This suggests that XRD can clearly identify whether a new crystalline phase has formed or not, as well as provide important information about structural changes in the tested compound. Overall, the use of X-ray diffraction provides valuable insights in detecting the formation of new crystalline phases that can affect the physicochemical and pharmacological properties of compounds, making it crucial in the development of more effective drug formulations.

3.4. Monitoring Polymorphic Phase Transformations

XRD is also used to monitor polymorphic phase transformations under various conditions. One relevant study is the research by Goloveshkin et al. (2021), where XRD was used to characterize a new polymorphic form of favipiravir obtained through recrystallization from ethyl acetate. The resulting diffraction pattern was used to index the new form and prepare a model for solution and structure refinement (Goloveshkin et al., 2021).

The XRD results showed that favipiravir underwent a partial transition from the metastable tetragonal polymorph to the orthorhombic polymorph during the heating process. This transition was identified through significant changes in the diffraction pattern, including changes in intensity and peak positions at specific temperatures. XRD successfully detected these changes, highlighting the crucial role of this technique in identifying significant structural changes in drugs, which can ultimately affect their pharmacological properties (Goloveshkin et al., 2021). This finding underscores the ability of XRD to characterize drug polymorph forms and monitor structural changes during formulation, demonstrating the great benefits of XRD in tracking crystal changes under various physicochemical conditions in the drug development process.

3.5. Challenges and Limitations in the Application of XRD

Based on the review results, one of the main limitations of XRD is its inability to effectively detect amorphous phases, as these phases do not produce clear diffraction patterns. As a result, structural changes in the amorphous phase are often undetected. For example, in the study by Fadhila et al. (2022), XRD was used to analyze polymorphic changes in celecoxib during the co-grinding process with the polymer PEG 4000. Although XRD showed a decrease in the intensity of crystalline peaks, it could not reveal detailed changes in the amorphous phase (Fadhila et al., 2022). This made it difficult to assess the degree of amorphousness in the solid dispersion of celecoxib. After the co-grinding process, the intensity of celecoxib's crystalline peaks decreased, but information regarding the formed amorphous phase remained undetectable. To gain a more comprehensive understanding of structural changes in the amorphous phase, additional techniques such as DSC (Differential Scanning Calorimetry) or NMR (Nuclear Magnetic Resonance) are needed (Fadhila et al., 2022). Therefore, while XRD provides a general overview of changes in crystallinity, other techniques are essential for a thorough assessment of changes in the amorphous phase and their impact on physical properties, such as solubility and dissolution rate.

Furthermore, XRD results are highly dependent on sample preparation. If the sample is not properly prepared or if there is uneven particle orientation, the resulting diffraction pattern may not be representative, thus affecting the accuracy of the analysis (Fadhila et al., 2022). To address this limitation, additional characterization techniques such as Fourier Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) are necessary. FTIR can provide information on the chemical interactions between celecoxib and PEG 4000, as well as help identify functional groups present. Meanwhile, SEM allows for the analysis of surface morphology of the solid dispersion, providing insights into the physical changes that occur during the preparation process (Fadhila et al., 2022). By combining the results from these various techniques, researchers can obtain a more comprehensive understanding of the physicochemical properties of the celecoxib–PEG 4000 solid dispersion system, thus improving the effectiveness of the drug formulation (Fadhila et al., 2022).

The complexity of the pharmaceutical compound's structure also often presents a challenge in identifying different polymorphs. In many cases, compounds with complex structures may not provide clear diffraction patterns when analyzed by XRD. Therefore, additional analyses such as Differential Scanning Calorimetry (DSC) or FTIR spectroscopy are necessary to support the results obtained from XRD. For example, in the study involving the characterization of piroxicam co-crystals, DSC analysis was used to determine the melting point and enthalpy changes, providing additional information about the interactions between components in the solid state (Imanto et al., 2023b). Additionally, FTIR spectroscopy was used to detect interactions between the drug and carrier, which is very helpful in understanding the physicochemical properties of the compound (Najih et al., 2021).

Thus, the use of additional analytical techniques is crucial to provide a more complete picture of the structure and properties of complex pharmaceutical compounds and to ensure that polymorph identification is accurately conducted.

3.6. The Role of XRD in Drug Development and Its Future Potential

X-ray diffraction (XRD) has become an essential tool in the pharmaceutical industry, particularly for ensuring the quality and safety of drugs. Its application in identifying stable crystal forms and optimizing solubility is crucial for the development of effective pharmaceutical products (Fawcett et al., 2019). XRD's ability to characterize polymorphism, where a compound can exist in various crystal forms, plays a key role in drug formulation and performance. Identifying different polymorphic forms can lead to variations in solubility and stability, which directly impact therapeutic efficacy (Bunaciu et al., 2015).

One of the main advantages of using XRD in pharmaceutical development is its ability to analyze the crystallinity of drug compounds. The transition from a crystalline form to an amorphous form can significantly enhance the solubility of poorly soluble drugs. Research has shown that the amorphous forms of drugs exhibit higher solubility compared to their crystalline counterparts (Hilaliyati et al., 2017). For example, Hilaliyati et al. demonstrated that the solid dispersion of amorphous ketoprofen-HPMC E6 has thermodynamic advantages over its crystalline form, leading to improved solubility (Hilaliyati et al., 2017).

Moreover, advances in XRD technology are expected to improve the resolution of structural analysis and expand the scope of polymorphic characterization. The integration of XRD with other techniques, such as neutron diffraction, has been proposed to enhance the understanding of complex pharmaceutical systems (Bunaciu et al., 2015; Fawcett et al., 2019). This combined approach allows for a more comprehensive analysis of drug formulations, enabling researchers to more effectively identify and optimize the physical properties of drugs.

The future of XRD in drug development also includes its role in real-time monitoring of the crystallization process. Techniques like XRD can provide valuable insights into the kinetics of polymorphic transitions during drug formulation, allowing for better control of the crystallization process (Schmitt, 2017; Takahashi et al., 2017). This capability is crucial for ensuring consistency and quality in pharmaceutical products, as variations in crystallization can lead to significant differences in drug performance.

4. CONCLUSION

The conclusion of this review article emphasizes that the X-ray Diffraction (XRD) method is highly useful in analyzing the polymorphism of pharmaceutical compounds. XRD is capable of identifying various crystal forms in drug compounds that can affect solubility and stability. The review findings show that XRD can be used for several purposes, such as identifying polymorphism, characterizing polymorphic changes, detecting new crystalline phases, and monitoring polymorphic phase transformations.

Although beneficial, XRD has some limitations, including difficulties in detecting amorphous forms and its results being highly influenced by sample preparation. As a result, XRD is often combined with other methods, such as DSC and FTIR, to provide more comprehensive analytical results.

Overall, XRD has proven to be an important tool in drug development, helping to ensure the quality and effectiveness of medications. In the future, XRD is expected to advance further, including its use for directly monitoring crystallization processes and optimizing drug quality control by identifying the most stable and effective crystal forms.

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