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Review Article

Exploring the world of x-ray diffraction and crystallography

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Abstract

A solid's qualities are directly impacted by the way its molecules are arrangedwithin. Consequently, creating connections among arrangement and attributesand creating practical materials require a grasp of the three-dimensional structure of matter. For the last century, X-ray crystallography has been the go-to technique foraccurately defining molecular structure at the atomic level. A basic analytical technique that is frequently useful in the creation of new drugs is crystallography. Its characteristics include atom size, length, electrondensity, atom mean position, and so forth. It is a precise approach foranalysing and identifying the molecule and molecular arrangement of crystals. The technique by which an x-ray beam scatters or distributes into multiple directions and assumes distinct patterns or forms as a result of the existence of crystalline particles is known as X-ray diffraction (XRD).X-ray diffraction and the crystallography technique are valuable in many different fields, including the pharmaceutical industry, nanotechnology, geology, electronics, mineralogy, geosciences, materials science, and medicine. These and other fields have rapidly advanced due to structural understanding derived from crystallographic studies.

Keywords: Bragg's law, Crystallography, Diffraction, Diffraction methods, X-ray

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1. Introduction

1.1. X ray

The electromagnetic radiations (EMR) with wavelengths between 10-3 nm and 10 nm are referred to as X-rays. Since their properties were unknown in 1895 when W. Rontgen made his discovery of X-rays, they were given that name.[1] In comparison to UV light, X-rays have substantially higher energy and shorter wavelengths. These are helpful for taking pictures of the human body since they can see through a person's skin to the bones underneath it.[1] Hard X-rays are those with wavelengths below 0.1 and 0.2nm, and soft X-rays are those with longer wavelengths. Hard X-rays are the type of X-rays used inmaterial analysis.[2]

1.2. Diffraction phenomenon

The diffraction of light had already been known before X-rays were discovered. The term "diffraction" describes a number of phenomena that happen when a wave runs into a slit or an obstruction. The diffraction phenomena are defined in classical physics as the spreading out of waves flowing through small holes and the bending of waves around small obstructions.[2]

2. X-ray Crystallography

The major technique for accessing the arrangement of the molecule or atom is X-ray crystallography. The three-dimensional structure and x-ray crystallography procedures are accurate, providing a three-dimensional structural

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parameter that is important for drug design and enabling functionalresearch that are structurally based.[3]

A concentrated amount of a refined substance crystallizes, and the crystals are subsequently exposed to an x-ray beam. Subsequently, the diffraction patternsthat have been processed can be utilized to obtain more information regarding the symmetry of the crystal packing and the dimensions of its repeating unit.[4]

2.1. X-ray diffraction

One technique that is non-invasive is X-ray diffraction (XRD) also aids in understanding how atoms are arranged, how these configurations can affect the behavior of materials, or how they can be utilized to ascertain the structure of complicated compounds.[5] Additionally, XRD is helpful in evaluating the qualitative and quantitative identification of different chemical compounds, assessing the intensity or degree of crystallinity of compounds, and identifying stacking faults (it is a type of defect). The examination of different compound features, such as particle size, polymorphism, isomorphism, phase transition, etc., is frequently done using XRD.[3] XRD has various types and one of commonly used is PXRD / XRPD. X-Ray Powder Diffraction (XRPD) provides firsthand knowledge into the elements and their physical and chemical characteristics.[6]

3. Background of X-ray diffraction and crystallography

Numerous groundbreaking works led to the development of X-ray crystallography as a technique for precise solid-state substance analysis. W.C. Roentgen made the discovery of X-rays in 1895. M. von Laue proved in 1912 that single crystals may diffract X-rays, and for this work the Nobel Prize in Physics was given to him in 1914 (Friedrich W, Knipping P, Laue M, 1912). The diffraction law known as Bragg's law was developed by W.L. Bragg, whoalso demonstrated how to use a diffraction pattern to determine the crystal structure of NaCl.[7] Instruments for observing diffraction patterns were firstdesigned by his father, W. H. Bragg, who was a pioneer in the field. The diffraction pattern and their combined and individual diffraction patterns were analyzed using Bragg's law. The father and son Braggs received the 1915 Physics Nobel Prize as a result of this.[8]

3.1. Principle of X-ray diffraction crystallography

A unidirectional X-ray beam focuses on the object being examined in order toresolve details of structure within the lattice of the crystal. The materials typically consist of crystallized repeating homogeneous atomic planes. Typically, a specific tube called a cathode ray tube is used to producepolychromatic X-rays. When polychromatic X-rays are passed via a monochromators, monochromatic radiation is created, which distinguishes the scattered, transferred, & absorbing rays upon reaching their atomic structures. [9] In a sealed tube with a vacuum atmosphere, X-rays are created. When 15–60kilovolts of current are applied inside the tube, electrons are produced that hitan anode made of Cr, Fe, Co, Cu, Mo, or Ag and produce X-ray beams.

Bragg's law states that incoming X-rays react with the specimen's atomic layers to produce diffracted, transmitted, refracted, scattered, and absorbed beam.

$$n\lambda = 2d \sin\theta$$

Where,

λ- Wavelength of the ray

θ – Angle between incident rays and surface of crystal.d – Spacing between layers of atoms

Constructive interference occurs when n is integer / whole no. [3]

This equation dealt with the relationship between electromagnetic radiation, the crystal sample's lattice spacing (the physical size of a unit cell in a crystallattice), and the diffraction angle. We have identified, analyzed, and counted these diffracted x-rays. Using a range 2θ angle to scan the sample. Lattice diffraction should occur in every direction that is practical. Since every mineral has a unique set of d spacing, changing the diffraction peak to d-space enables mineral identification. Typically, a difference of d spacing with a standard reference sample is used to achieve it. [3]

3.2. Bragg's law of diffraction

W.L. Bragg thought of X-ray diffraction through the surface of a crystal as an obstacle of reflecting X-rays across the atomic structures of the minerals in line with the principles of reflection with the objective to comprehend the diffraction of X-rays.

When X-rays that have been scattered, react constructively with one another at certain wavelengths with particular incidence angles, they form powerful reflecting X-rays. In order for constructive interference to occur, the differences in the electromagnetic paths must be an integer number of the wavelength. When this constructive interference occurs, a scattered X-ray beam escapes the crystal at an angle corresponding with the angle of the incident beam. [11]

Think of a collection of perpendicular planes of atoms in the crystal that haveMiller indices and a spacing of d among each succeeding surface. Assume the incident rays of a straight beam of X-rays that are monochromatic of wavelength λ lay in the horizontal direction of the substrate at a striking pointθ.

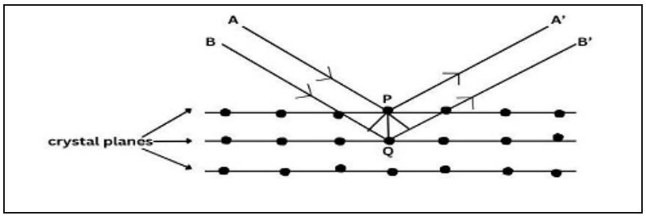

Figure 1: Explanation of bragg's law

Allow AP and BQ to be two adjoining incident rays that follow PA' and QB',respectively, after reflecting on points P and Q on the Crystal surfaces. The highest value can be seen whenever the route variance between APA' and BQB' is an integral multiple of λ, indicating the presence of constructive interference.[10]

3.3. Advantages of X-ray diffraction crystallography

Strong and quick (less than 20 minutes) method for identifying an unidentified element.
In most cases, it provides an unambiguous mineral determination.
XRD units are widely available.
Data interpretation is relatively straightforward.
Requires minimal sample preparation
Highly sensitive (the quality of being sensitive)
Non corrosive, steady character/nature
Easy to prepare Sample/material
Easy to handle or use
Cheap maintenance
Work High/fast speed.
Glancing angle.
Effective design.
Labour- saving system/ convenient.
A system automatically operates.
Useful for identification of purity of the sample

3.4. Applications of X-ray crystallography

1. The primary application of X-ray powder diffraction is for the determination of unidentified mineral crystals (elements, inorganic chemicals, etc.).
2. Research findings in geology, environmental science, material science, engineering, and biology depend on determining the presence of unidentified substances.
3. Utilized to detect minerals with fine grains that are challenging to distinguishvisually, such as clays and mixed layer clays.
4. To calculate the circumference of the unit cell.
5. For determining the crystal's fundamental composition.
6. It is employed to quantify textural features in a polycrystalline specimen, which includes grain orientation.

By employing advanced methods, X-ray diffraction (XRD) may be utilized to quantify mineral quantities as well as identify the arrangement of crystals through Rietveld refinement.

3.5. To be particular about pharmaceutical field

Drugs come in a range of shapes and compositions, including tablets, pills, capsules, and aerosol sprays. An individual medicine can be manufactured inhundreds of approaches to improve its capacity to penetrate the circulatory system and deliver treatment to a particular area (skin's lotion, nasal spray, anti-itch, anticancer, etc.) and for it to function immediately or over time. A dosage form might increase the medication's shelf life, provide stomach buffering, enhance its flavour, or be a component of the plan for the drug's timed release into the bloodstream.

Pharmaceuticals' chemical makeup can be clearly identified using XRD. The crystal structures found in the medication under investigation directly influence the XRD pattern. As a result, it is easy to retrieve the parameters generally linked to crystal structure.

An X-ray powder diffraction pattern is required for examining the structure of the crystal, get a patent, and safeguard the investment made by the business. When it comes to multicomponent formulations, it is possible to accurately assess in vivo the proportions of the active ingredients in the final tablet formas well as the proportion of the various amorphous packing materials used.[12]

XRD also possess various important application in different fields such as: -

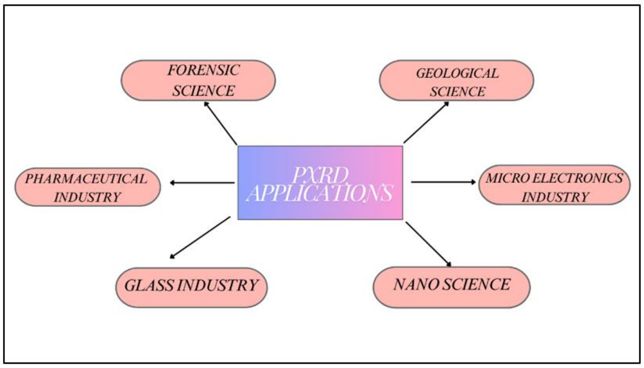

Figure 2: Various application of XRD Instrumentation of XRD

3.6. Diffractometer

A diffractometer is a very accurate device with two independent rotational axes. With the aid of this apparatus, we are able to determine an X-ray beam's intensity data as a function of angle and to satisfy Bragg's law for X-rays with known wavelengths. [13] The primary three elements of an X-ray diffractometer are an X-ray tube, a sample holder, and an X-ray detector. By employing a filament that has been burned to create electrons, a voltage is applied to speed up the electrons towards a target, and the rapidly moving electrons attack the material of interest generating X-rays in a cathode ray tube. Once electrons possess enough force to remove the innermost electronsof the target material, characteristic X-ray spectra appear. Of the several components that comprise these spectrums, Kα and Kβ are particularly abundant.

Part of Kα is composed of Kα1 and Kα2. Compared to Kα2, Kα1 has a slightlybriefer spectrum and is twice as strong. The specific wavelengths (Cu, Fe, Mo, and Cr) correspond to the target material. Filtering with foils or crystal monochrometers needs to generate monochromatic X-rays for diffraction to take place. Since Kα1 and Kα2 have suitably near wavelengths, a weighted mean of them is used. Copper is a commonly frequently employed target material for single-crystal diffraction, with a Cu Kα radiation of 1.5418 A. Focused X-rays will be applied to the specimen. When the specimen and sensor are spinning, the intensity of the reflecting X-rays is determined.

Oncethe object being photographed is impinged upon by the reflected X-rays' geometry, Bragg's law is achieved. This radiation from X-rays is detected and processed by a detector. After that,the data is transformed into a count rate and sent to a computer monitor or printer. The object being studied revolves at an angle u in the course of the collimated X-ray beam in an X-ray diffractometer, while the X-ray detector turns at an angle of 2θ to collect the scattered X-rays. The tool employed to retain the position and spin the material is called a goniometer. In conventional particle patterns, statistics are collected at 2θ from 5 to 70◦, angles which are set in the X-ray scanner.[12]

4. X-ray Diffraction Method

The x-ray diffraction behavior is helpful in determining the composition of solids. Additionally, for the X-ray spectrum investigation. Bragg's principle isoften applied in such two scenarios for determining the crystal arrangement using Bragg's law[10]. Additional constant range of wavelengths, λ or θ, is given to enable to do thispractically. In other words, given an amount of the inclination "θ," the value of λ is randomly selected. In general, three approaches are used to examine the structure of molecules. These are the powder method, Laue method, and Rotating Crystal method.

4.1. Laue method

This is among the crucial techniques. Essentially employed to determine crystal symmetry, this tool is utilized for examining crystal structure.[10]

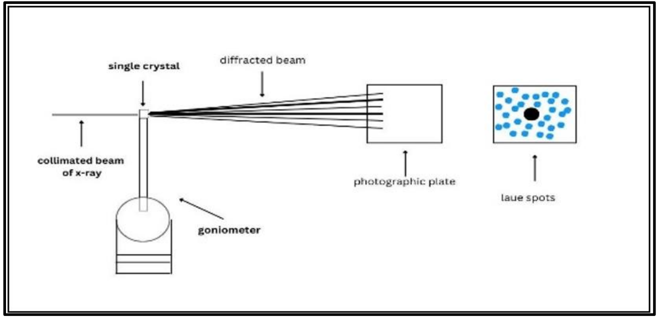

Figure 3: Laue method of XRD

In this procedure, a tiny crystal measuring 1 mm x 1 mm x 1 mm is put on a goniometer and exposed to a stream of polychromatic X-rays with frequenciesthat vary from 0.2Å to 2Å. The crystal's alignment with regard to the X-ray beam is capable of being altered by rotating the goniometer. Usually, the beamis let pass through parallel to the crystal's plane of analysis [10].

When you traverse the crystal. The X-ray hits many Bragg's planes with d intervals between them and creating various angles "θ" with relation to the X-ray's incidence source. When λ and θ meet the Bragg's condition, then

$$2d \sin\theta = n\lambda$$

For a given value of d.

A diffraction pattern is produced by constructive interference and results in a rise in strength in particular planes. A photographic plate placed on the contrary edge of the crystal will show this diffraction pattern. The pattern of diffraction found on the picture plate, comprises of a symmetrical spot layout based on the crystal lattice's symmetry characteristic. Typically, the degree of symmetry is found using the Laue technique.[10]

4.2. Rotating crystal method

Using this technique, a single, one-millimeter crystal is fixed to a revolving shaft, such that the spindle's rotational axis and one of the crystal's axis overlap. A monochromatic X-ray beam hits the substance parallel to the spindle's rotational axis.

A hollowed tubular container with an axis that is intersecting with the shaft'saxis covers it, such a way that the crystal is positioned in the middle of the cylindrical holder, in order to acquire the pattern of diffraction. The surface of the cylindrical container has a photographic plate affixed to it. Note that the axis of motion is typically assumed to be the vertical direction.

Diffraction of x-rays will occur when the crystal rotates. Whenever the Crystalplane's position with relation to X rays, in a manner that satisfies Bragg's Condition. Every crystal axis that is parallel to the spindle's rotational axis. The incident ray should be divided into a horizontal surface that is parallel to the shaft. On the other hand, the plane that includes the X-ray incident stream will not exhibit any scattering.[10]

4.3. Powder crystal method

One crystal has to be precisely mounted on one crystal axis in order to use Bragg's technique and the rotating Crystal technique. It is a laborious processto do. The powder crystal approach is utilized to get around this problem. Independent of one another, Deby, Scherer, and Hull devised this technique.The crystalline material is crushed into a powder using this process, which causes the crystallites to adopt a random orientation. A tiny capillary tube is filled with a sample of powdered powder, constructed of non-diffracting substance or, with the aid of non-diffracting binding substance, the sample issimply adhered to a hair. It is put in the line of a thin, monochromatic X-ray beam**.** Although there are additionally many crystallites with erratic orientations, the underlying premise of the crystal technique is this. For Bragg's diffraction to occur, that is, for the diffraction to happen in line with the requirement.

$2d \sin\theta = n\lambda$,

Where λ is a constant in this instance, all potential diffraction plains must be accessible.

As a result, a collection of parallelograms that are angled at different angles towards the x-ray beam will produce the reflected image.[10]

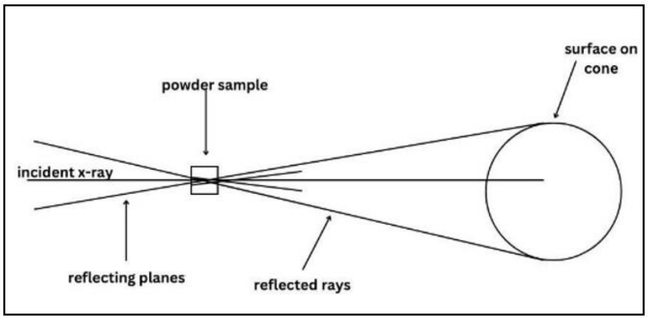

Figure 4: Powder crystal method of

Small Angle X-ray Scattering (SAXS).

This approach explores the field of solution-based research, revealing the parameters and nature of macromolecules. SAXS was essential in exposing the constant modifications to the structure of proteins such as calmodulin in the analysis of protein conformational changes. Even though it might be difficult to precisely identify molecule shapes via scattered data, SAXS is nevertheless a useful technique for comprehending solution structures.[14]

5. Impactual Discoveries by Crystallography

The significance of X-ray diffraction and its uses in various research domainshave resulted in the granting of 29 Nobel Prizes to date. The United Nations has recognized the effective introduction of crystallography into several scientific domains by designating 2014 as the International Year of Crystallography.[15] Therefore, it is crucial to highlight a few groundbreaking findings that increased crystallography's significance.

A diamond's geometry made crystallography's role in understanding material characteristics clear after the first crystal structure of NaCl was identified by X-ray diffraction. A repeating quadrilateral arrangement of carbon atoms in the crystal lattice was found to be the cause of diamond's extreme hardness.[16] Hexamethylenetetramine, quartz, and hex methylbenzene were among the next substances whose structures were determined. W.H. Barnes structural research on water were crucial in giving clear explanations of hydrogen bonding in water crystals in the late 1920s.[17] Since that time, when it comes to examining the three-dimensional configuration of many other materials, such as elements, binary compounds, as well as proteins, X-ray diffraction has shown to be a trustworthy technique.

J. D. Bernal and colleagues gathered the first X-ray diffraction images of pepsin, a tiny hydrated protein, in 1934.[18] About 25 years later, J. Kendrewet al. and M. Perutz et al. discovered the crystal structures of myoglobin and hemoglobin, respectively, and were honoured with the Nobel Prize in Chemistry in 1962. Many biological compounds, including insulin (1954), penicillin (1949), vitamin B12 (1954), and cholesterol (1937), were solved by D.C. Hodgkin (1969). In 1964, she received the Chemistry Nobel Prize in recognition of her ground-breaking works.

The finding of the blueprint for DNA by J. D. Watson and F. H. C. Crick, which was based on diffraction tests conducted by R. Franklin, was one of the most significant achievements of the twentieth century.[19] Along with M. Wilkins, who had collaborated with Franklin, Watson, Crick, and the other recipient received the 1962 Nobel Prize in Physiology. The "double helix" discovery made macro molecules and protein crystallography possible, which are now vital resources in the biology and medical disciplines.[20]

5.1. Need of X-ray diffraction and crystallography

A molecule with medicinal promise must pass several obstacles in the form of time, money, and human resources before it can be brought to market. This is a demanding procedure. It might take up to 20 years for a single chemical to be authorized as a medication, and research and development expenses can range from $2 to $3billion.[19] The scientific setting for drug development has changed between a focuson phenotypic identification or empirical assessment of potential therapies toan emphasis on biological avenues in order to aid expedite the procedure andreduce the duration and effort needed for clinical testing and safety authorization.[21]

When combined alongside other identical techniques, X-ray structural analysis methods such as single crystal X-ray diffraction (SCXRD) andpowder X-ray diffraction (PXRD) using the pair distribution function (PDF) have significantly aided in the conceptualization of biomimetic drugs alongside the continual assessment of drug stability. In the past, X-ray diffraction (XRD) has been the most popular method for identifying various structural characteristics in drug molecules. It has been helpful in the creation of specific biomolecule-ligand complexes, drug- receptor interactions, and structure-based drug design (SBDD).[22]

The use of X-ray crystallography in drug design is crucial. The first step in developing a novel medicine to tackle a particular bacterium or virus is to identify a tiny chemical that can obstruct the enzymes and active proteins thatare responsible for attacking human cells.

Scientists can create pharmacological molecules that can clamp onto the protein's "active" location and so inhibit its detrimental function by knowing the exact shape of the protein. [8] With the advent of powerful X-ray sources (such synchrotrons), novel detectors, innovative approaches to research, and state-of-the-art programmes, the number of accurately identified crystal structures of small and macromolecules has increased dramatically.

More than 750,000 small molecule crystal structures can currently be found in the Cambridge Structural Database (CSD) [23] and over 105,000 bio macromolecule structures can be found in the Protein Data Bank, approximately 90% of which were determined using X-ray diffraction.[24]

Researchers could greatly improve X-ray crystallography by integrating AI approaches to more precisely and efficiently define macromolecular structures, find intriguing targets, and create novel medications. As a result, X-ray crystallography is well-positioned to continue playing a crucial part in discovering drugs as well as development into the coming years.[2]

5.2. Pros of XRD when compared with other methods

Mass spectrometry, NMR spectroscopy, and X-ray crystallography have recently taken the lead in the structure investigation of natural compounds. From an instrumental standpoint, the MS field has made significant progress. [26] In the last ten years, new technologies including MSI, REIMS, IM-MS, and AS-MS have emerged. These resources, particularly when used in tandem, could provide natural product chemists new, standardized techniques.

Increased use of X-ray diffraction methods is anticipated. Conventionaldiffractometer’s can determine the structure more easily from smaller particles or granulated specimens. In relation to speed, X-ray crystallographyought to potentially be better than NMR spectroscopy due to the growing availability of synchrotron sources worldwide and the falling costs of beamline time.

The full structure of a natural substance on the order of the size of taxol maynow be revealed by renting 2 hours of synchrotron measurement time. These120 minutes can cost between 2000 and 3000 EUR and cover data gathering, refinement, and evaluation. The same task might take one day on a typical laboratory diffractometer. On the other hand, the data collection and taxol interpretation for multidimensional NMR spectroscopy can require twice that time.[26]

A fundamental method in structural biology, X-ray diffraction (XRD) allows for the atomic defining of protein structures. XRD has been essential to comprehending the molecular machinery of life since the first protein structures have been discovered. As science has advanced gradually, XRD's precision and effectiveness have increased dramatically. The necessity to analyze small or additional complicated crystals, get higher-resolution frameworks, and quicker speed of research has propelled these developments. As a result, XRD is superior over alternative methods.[27]

6. Conclusion

X-ray crystallography has shown to be a very useful technology in the pharmaceutical research. In this article, the benefits of employing x-ray diffraction and crystallography are reviewed, with a focus on their applications in the pharmaceutical industry. A theoretical examination of several x-ray diffraction methods is presented, along with an explanation of why XRD is necessary. Various discoveries made possible by crystallography are examined and assessed.

7. Source of Funding

None.

8. Conflict of Interest

None.

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