XRD (X RAY DIFFRACTION) STUDY OF ANTIFUNGAL DRUG (KETOCONAZOLE)

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ABSTRACT

The frequent human exposure to various types of indoor lamps, as well as other light sources (televi- sion monitors, tablets and computers), raises a question: are there risks for the population? In the present study the emission of UVA and UVB radiation by lamps and screens of electronic devices were measured in order to determine the safe distance between the emitting source and the individual. We concluded that the lamps and electronic devices do not emit ultraviolet radiation; so they pose no health risk for the population.

Keywords: Ultraviolet Rays, Wavelength, X-Ray Powder Diffraction, Light.

I.   INTRODUCTION

Diffraction occurs when light is scattered by a periodic array with long-range order, producing constructive interference at specific angles. The atoms in a crystal are periodically arranged thus diffract light. The wavelength of X-ray are similar to the distance between atoms, Powder X-ray Diffraction (PXRD) techniques uses this principle to elucidate the crystalline nature of materials. The scattering of X-rays from atoms produce a diffraction pattern that contains information about the atomic arrangement in crystal. Amorphous materials like glass do not have periodic array with long-range order so; they do not produce any significant peak in diffraction pattern.

With recent recent developments within the field of fabric science technologies and creation of latest ingredients, it becomes essential to reinforce this substantial testing and analysis state of affairs to resolve the complex issues. One of such ways is XRD (X-ray diffraction), diffraction may be performance or a tool wont in calculate the atomic & molecular assembly of a mineral by means that of a diffracting beam through it altogether directions. At present, the aim of t the XRD device is to work out and analyze the section of a fabric, whether or not within the kind of powder or perhaps solid from inorganic samples, within the kind of transparent & amorphous. In the qualitative analysis, the data conferred is together with of 2 letter angels, ultimate Intensity, and therefore the quantity of lattice constant. For analysis, the information includes section analysis, which may be within the kind of identification of the sort of section, section composition (percentage), crystal size, orientation, et al (Monshi et al, 2012). In the analysis victimization XRD Instruments, the essential principle of XRD is to part light-weight through the crystal slit, optical phenomenon of sunshine hy lattices or crystals will occur if the optical phenomenon comes from radius that includes a wavelength cherish the gap between atoms, that is concerning one angstrom unit.

The radiation is employed within the kind of X-ray radiation, electrons, and neutrons. X-ray may be a gauge hos an with high energy that includes a wavelength starting from zeru.5 up to 2.5 Armstrong once Associate in Nursing X-ray beam interacts with a fabric, a number of the beams are going to be absorbed, transmitted, and a few of it's scattered diffracted. This scattered optical miracle is what XRD detects. The scattered X-ray beam is canceled one another out as a result of the sections square measure completely different and a few square measure reciprocally reinforcing as a result of the phase is that the same.

X-ray beams that reinforce one another square measure referred to as optical phenomenon beams, once X rays square measure discharged at the Bravais lattice of the fabric to be tested, the rays square measure diffracted and kind bound patterns referred to as fingerprints (Hakimetal, 2019: Bunaciu et al.. 2015). The application of this XRD instrument is extremely wide used. This XRD instrument is most frequently used for the identification of unknown crystalline resources (e.g., minerals, inorganic compounds). one amongst them is that the characterization of unknown. supplies victimization XRD tools is extremely helpful for studies in earth science, ecology, materials science, engineering, and biology, different applications of XRD instruments square measure the characterization of crystalline materials, identification of fine-grained reserves, determination of unit dimensions, and measure of sample purity (Bunaciu et al, 2015; Alexander & Klug, 1948, Zhou et al.

Limitations

- Homogeneous and single-phase material is best for identification of anunknown.
- Access to a standard reference file of inorganic compounds is required.
- Material, in tenths of a gram quantity, must be ground into a powder. For mixed materials, detection limit is $\sim 2\%$ of sample.
- For unit cell determinations, indexing of patterns for non- isometric crystalsystems is complicated.
- Peak overlay may occur and worsens for high angle "reflections"

Applications

- Qualitative and quantitative phase analysis of pure substances and mixtures. The most common method for phase analysis is often called 'X-ray powder diffraction' (XRPD).
- Analysis of phase changes under other special conditions such as temperature, humidity and applied pressure (non-ambient studies).
- Analysis of physical properties such as crystallite size (diameter), crystal orientation, and residual stress, which together are called the 'microstructure' of polycrystalline materials.
- Many of these techniques can also be used for polycrystalline layered materials such as coatings and thin films using a method called grazing incidence XRD (GIXRD). Studies ofsmall areas in polycrystalline materials employ a method called micro-diffraction.
- Other X-ray diffraction techniques for materials that are not polycrystalline (for example single crystal semiconductor wafers or epitaxial layers) include high-resolution analysis of hetero-epitaxial layers (HR-XRD). The analysis of these make use of Bragg's Law, dynamical diffraction theory, and single crystal orientation, for both wafer as well as ingots.
- Differentiation between crystalline and amorphous materials.
- Determining the grain/particle size of the material.
- Determining the degree of texture (preferred orientation of grains) in material.
- Determination of the texture of poly-grained materials.
- Measurement of sample purity.
- Determination of orientation of single crystals.
- Determination of electron distribution within the atoms and throughout the unit cell.
- Determination of molecular structure and characterization of proteins and nucleic acid.
- Determination of unit cell dimensions.
- Whether the sample is a composite material consisting of multiple crystallographic phases and, if so, determine the fraction of each phase.

II.　AIM & OBJECTIVES

Aim: XRD (X-ray diffraction) study of Antifungal Drug (ketoconazole)

Objectives

- Relationship between structures of engineering materials.
- To understand the classification of crystals.
- To understand mathematical description of ideal crystal.
- To understand Miller indices for directions and planes in lattices and crystals.
- To understand how to use X-Ray Diffraction for determination of crystal geometry.
- Understand the concept of diffraction in crystals.
- Be able to derive and use Bragg's law.
- Know how X-rays are produced.
- Know the typical emission spectrum for X-rays, the source of white radiation and the Kand KB lines.

- Know about Compton scattering. understand the concept of diffraction in crystals

ADVANTAGES:

- Measurement under atom sphere pressure
- XRD is Nondestructive technique, easly sample perp.
- X-ray are not observed very much by air, so the speciman need not be in evacuated chamber
- Probe depth controle by incidence angle
- X-ray diffraction structure analysis can be applied for single crystal
- All structure information is in reciprocal space we lect and measure HKL intensities, then solve ad refine a crystal structure

DISADVANTAGES:

- X-rays do not interact very strongly with lighter elements.
- X-rays are hazardous to use.
- XRD has size limitations. It is much more accurate for measuring large crystalline structures rather than small ones. (smaller ones that are present only in trace amounts willften go undetected by XRD readings)

III.   PLAN OF WORK

1) Literature Survey
2) Selection of ketoconazole API
3) Compatibility study of ketoconazole
- XRD(X-ray diffraction)
4) Identification of ketoconazole API:- XRD
5) Evaluation Of ketoconazole
- Appearance
- IUPAC Name
- Colour
- Molecular formula
- Melting point
- BSC class
- Dissolution constant
- Half life
- Solubility
- Dose
- XRD Graph
- Percentage of compound present
6) Conclusion

IV.   XRD INSTRUMENTATION

Instrumentation

Max von Laue and Co., in 1912, discovered that crystalline substances act as three-dimensional diffraction gratings for X-ray wavelengths similar to the spacing of planes in a crystal lattice (Friedrich et al., 1912). X-ray diffraction is now a common technique for the study of crystal structures and atomic spacing. X-ray diffraction is based on constructive interference of monochromatic X-rays and a crystalline sample. These X-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample.

X ray Diffraction Principle

X-ray diffraction is based on constructive interference of monochromatic X- rays and a crystalline sample.

These X-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. When a monochromatic x-ray incident occurs on a crystal. The atomic electrons in the Crystal are sent into vibration. With the same frequency as that of the frequency of the incident ray and are accelerated. These Accelerated electrons then emit the radiation of the same frequency as that of incident x-rays in all directions.

If the wavelength of incident radiation is large compared to the dimensions of the Crystal. Then the radiated X-ray are in phase with each. But since the atomic dimension are nearly equal to the wavelength of X-Ray. The radiation emitted by the electrons is out of phase with each other. These radiations may interfere constructively or destructively producing a diffraction pattern (i.e. maxima and minima) in certain directions.

Bragg's law:

Bragg's law is a special case of Laue diffraction, which determines the angles of coherent and incoherent scattering from a crystal lattice. When X-rays are incident on a particular atom, they make an electronic cloud move like an electromagnetic wave. The movement of these charges radiates waves again with similar frequency, slightly blurred due to different effects, and this phenomenon is known as Rayleigh scattering. Basically, this law explains the relationship between an x-ray light shooting and its reflection from a crystal surface.

Brag's Law states the following:

When the X-ray is incident onto a crystal surface, its angle of incidence, θ, will reflect with the same angle of scattering, θ. And, when the path difference, d is equal to a whole number, n, of wavelength, λ, constructive interference will occur. The exact process takes place upon scattering neutron waves via nuclei or a coherent spin interaction with an isolated electron. These wave fields that are re-emitted interfere with each other destructively or constructively, creating a diffraction pattern on a film or detector. The diffraction analysis is the resulting wave interference, and this analysis is known as Bragg diffraction.
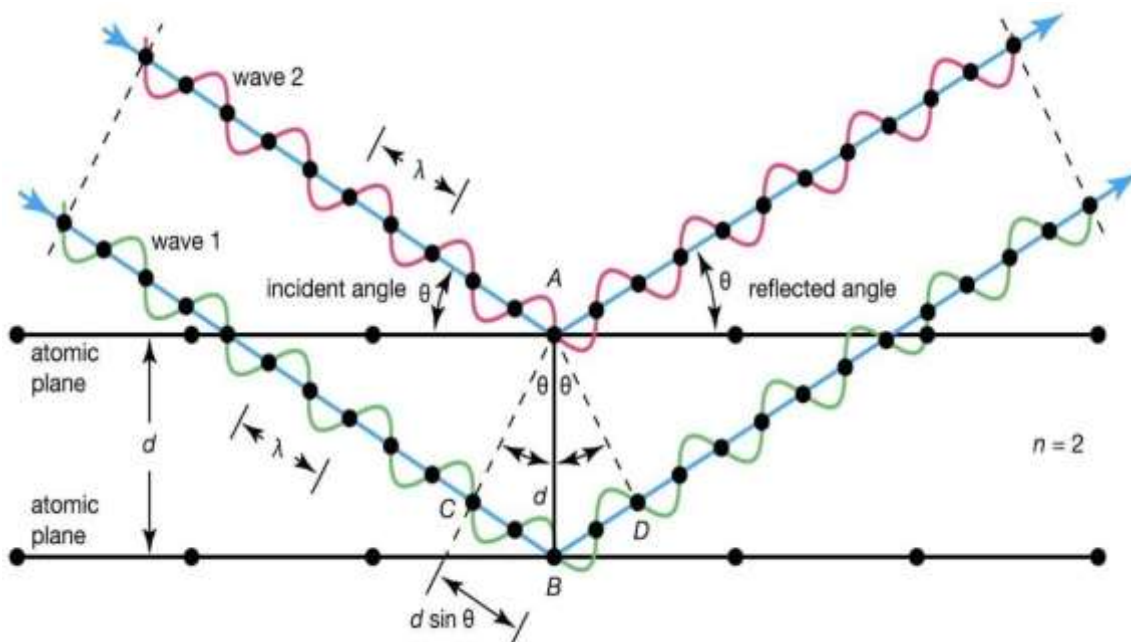

Fig 1: Brag's Law

This observation illustrates the X-ray wave interface, called X-ray diffraction (XRD) and proof of the atomic structure of crystals.

Bragg was also awarded the Nobel Prize in Physics for identifying crystal structures starting with NaCl, ZnS, and diamond. In addition, to understand the structure of every state of matter by any beam, e.g., ions, protons, electrons, neutrons, with a wavelength similar to the length between the molecular structures, diffraction was developed.

Derivation of Bragg's Law

Consider the following figure of beams in which the phases of the beams coincide when the incident angle is equal to the reflecting angle. The incident beams are parallel to each other until they reach point z. When they are at point z, they strike the surface and travel upwards. At point B, the second beam scatters. AB + BC is the distance travelled by the second beam. The extra distance is known as the integral multiple of the wavelength.
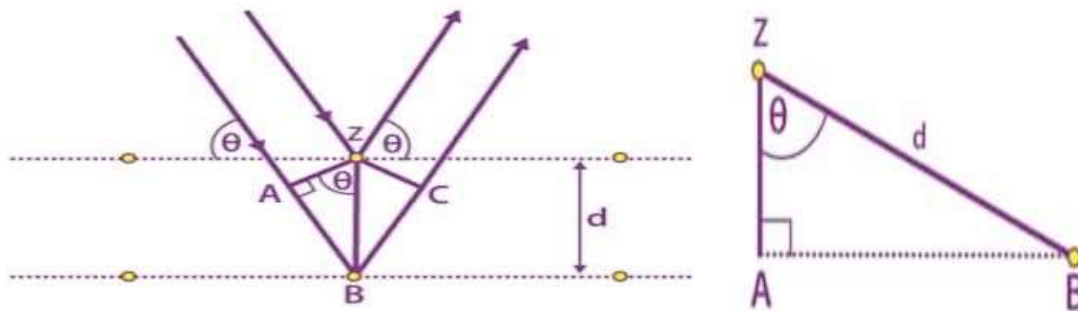
Fig 2: Bragg's Law Of Reflection

$n\lambda = AB + BC$

We also know that $AB = BC$ $n\lambda = 2AB$ (equation 1)

d is the hypotenuse of the right triangle Abz. Ab is the opposite of the angle θ. $AB = d \sin\theta$ (equation 2)

Substituting equation 2 in equation 1

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

The above equation is Bragg's law expression. Where,

A = wavelength of the x-ray

d= spacing of the crystal layers (path difference)

θ= incident angle (the angle between incident ray and the scatter plane) n= integer

λ=x-ray Wavelength

XRD INSTRUMENTATION CONSIST OF FOLLOWING PARTS:-
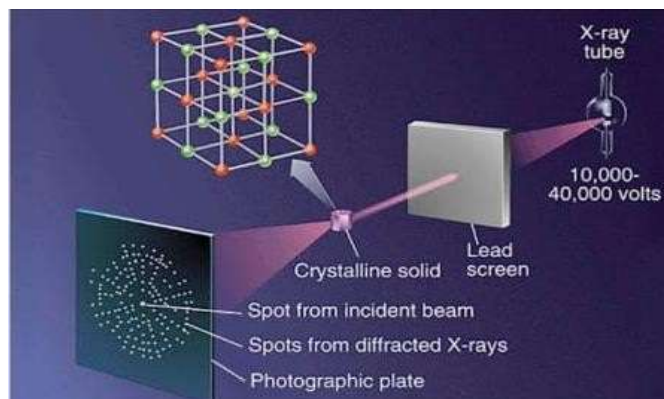
Fig 3: XRD INSTRUMENTATION

1) X-ray source/ X-ray tube

2) Collimator

3) Monochromator

A) Filters monochromator

B) Crystal monochromator

4) Detectors

A) Photographic detector

B) Counter detector

a) Geiger Muller tube detector

b) Proportional counter detector

c) Scintillator counter detector

d) Semiconductor detector

1) X-ray tube

X-rays are produced whenever high-speed electrons collide with a metal target.A source of electrons - hot W filament, a high accelerating voltage between the cathode (W) and the anode and a metal target, Cu. Al. Mo. Mg. The anode is a water-cooled block of Cu containing desired target metal.

Features & Functioning of XRT

- Composed of evacuated tube possessing cathode (tungsten filament) at one end & anode (metal target) at another end.

- Passage of current through tube causes tungsten filament to glow & emits electron.

- Among the two electrodes large voltage difference is applied, causing electrons to move at high velocity from filament and strike to anode.

X rays are generally produced in XRT.
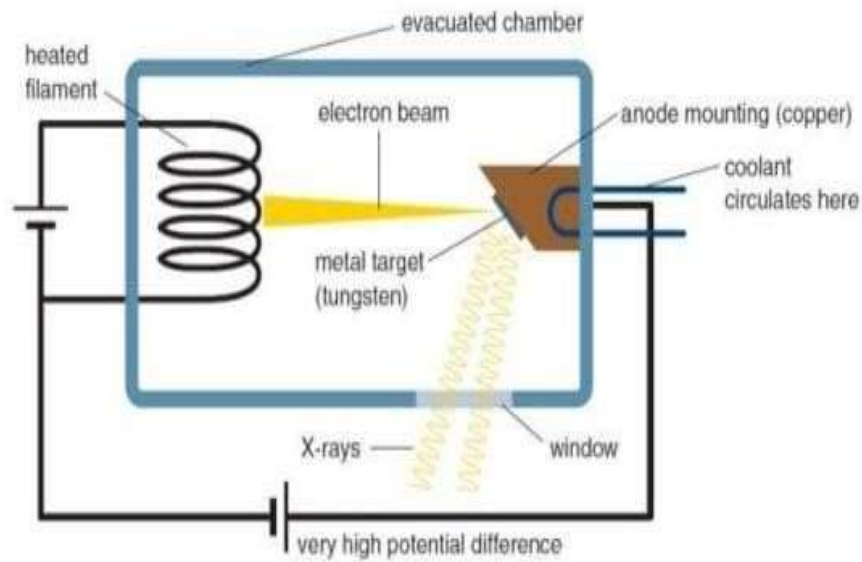
Fig 4: X-ray tube

Due to high velocity impact of electrons on the target, inner shell electrons of metal get dislodge, which causes the outer shell electrons to jump to a lower energy shell to replace the dislodge electrons. These electronic transitions results in the generation of X-rays. The produced X-rays are allowed to move through a window of X-ray tube.

2. Collimator

A device that is used for narrowing of a beam of particles or waves.

Collimator makes, random directional X-rays to be narrow and parallel. These are usually made up of tungsten, stainless steel and ceramics. Pitch ranges from 400microns to 6 microns.
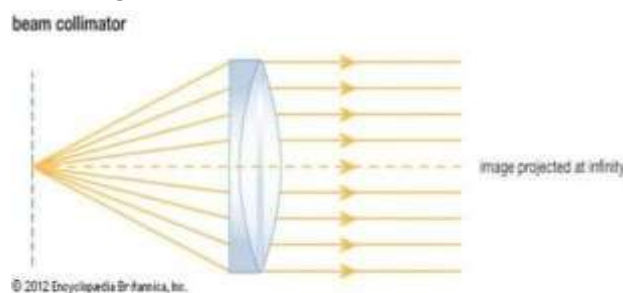
Fig 5: Collimator

3. Monochromator

A device that is used for removal of unwanted radiation.

1. Filters Monochromators
2. Crystal Monochromators

1. Filters Monochromators :-

Made up of specialized material that absorb unwanted radiation and passes the desiredradiation.

e.g X-rays produced from molybdenum are monochromatized by zirconium filters.

These zirconium filters absorb the molybdenum and allows to pass the k(beta) lines. For target element like copper, iron, cobalt, nickel the filters like Ni, Mn, & Co are commonly used.

2. Crystal Monochromators:-

These are the device that partially polarize a non polarized X-ray beam on the basis of Bragg'sdiffraction.

For broad band use: pyrolytic graphite materialFor narrow band use: Si, Ge or quartz

Types:

1. Flat Crystal
2. Curved Crystal
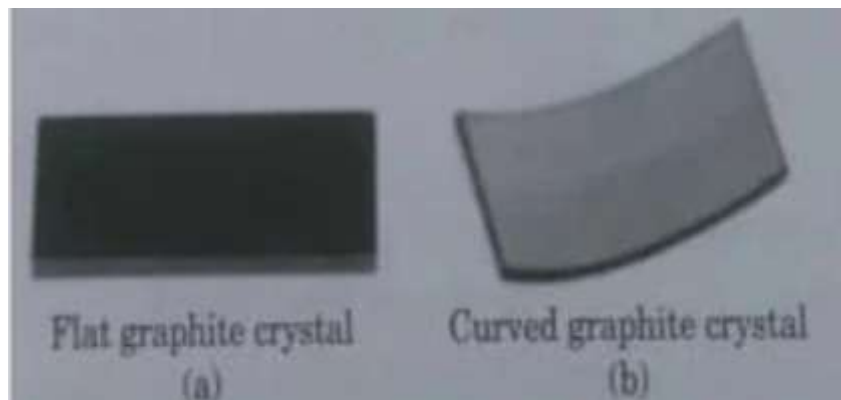
Fig 6: Images For Crystal Monocromaters

4. Detectors

X-rays can be detected using two types of detectors:

1. Photographic Detectors
2. Counter Detectors
a) Geiger Muller Tube Counter
b) Proportional Counter
c) Scintillator Counter
d) Semiconductor Detector

1. Photographic detectors

A plane or cylindrical film is used to determine the position & intensity of X-rays. Cylindricalfilms are developed by exposing the detectors to X-rays.The extent of blackening of developedfilm is expressed as density. Density is the direct measurement of X-ray energy which causes blackening of photographic film.

D = log.I/I

2. Counter Detectors

a. Geiger muller Tube Counter :-

It is composed of glass tube (19 mm dia). The tube is comprisedof a half metal cylinder of about 4 inches length, made up of copper. Along the axis of cylinder a thin metal wire of tungsten is tied. The cylinder & wire are connected to an electrical voltagesource. The tube is filled with gas, usually Argon at a low pressure .a voltage is set up betweenthe cathode and anode.

Working:

When X-rays enters the Geiger tube, a collision occurs between the gas molecule and X-rays. Thereby electrons are ejected out of atoms of neutral molecules of argon gas. This causes production of positive molecular ions and free electrons. These electrons being negatively charged, moves towards anode and positively charged argon ions moves toward cathode. A potential gradient is applied to accelerate electrons. This causes electrons to pick much energyto eject more electrons out of atom.
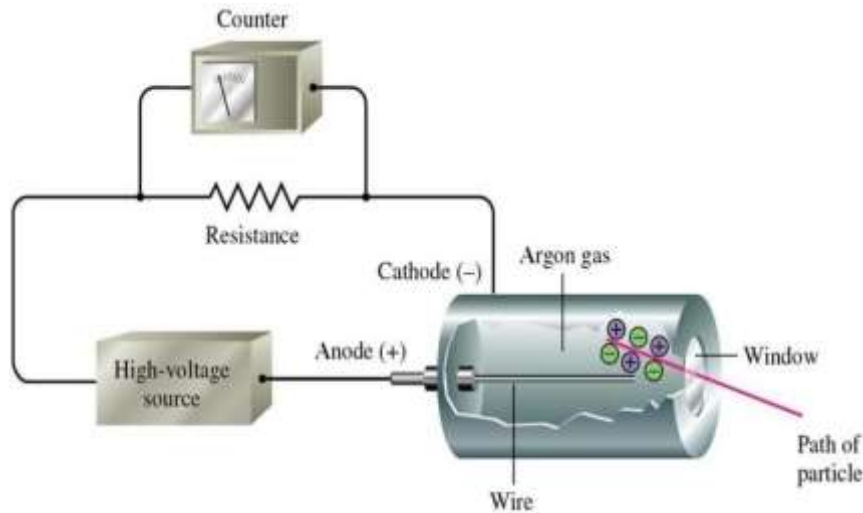
Fig 7: Geiger muller Tube Counter

Merits:

1. significant signals are obtained for a given X-ray intensity
2. Economical
3. Requires less Maintenance

Demerits:

1. Used for measuring low rate X-rays.
2. Low efficiency below 1angstrom
3. Unable to measure energy of ionizing radiation

Application:

1. To detect alpha, beta and gamma radiation from given sample
2. To check for environmental levels of radioactivity.

In risk assessment in various working places. To identify radioactivity in rocks and minerals.
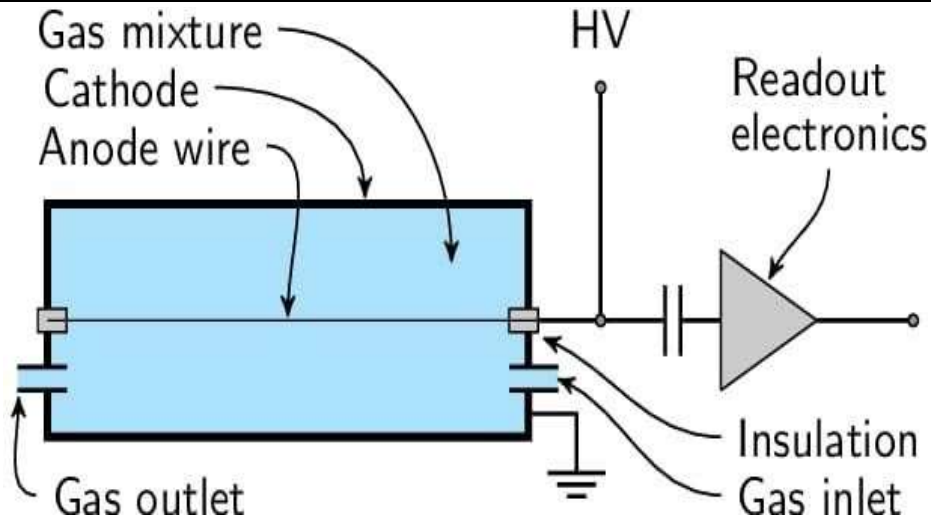
b) Proportional Counter:-

Similar in construction to Geiger-Muller Counter Heavy gas like P-10 or xenon or krypton isused.

Proportional counter is a combination of two ionization regions

a) lon drift region: region that exist in outer volume of the chamber.

b) Avalanche region: region that exist in the immediate vicinity of the anode.

A specialized circuit is connected to tube so that X-rays of particular energy can be measured. Therefore the output of proportional counter apparatus depends upon incident X-ray intensity.This in turn picks up further energy and libera even more electrons. Such a progressive pro is called avalanche. Positive ions hit the cathodic half cylinder with enough energy to eject further more electrons. Therefore avalanche of electrons incline on wire which is detected as a pulse of electric current. The electric pulse so generated indicates passing of a charged particle through the tube. This pulse can be read or measured through a meter.

Fig 8: Proportional Counter

Merits: count high rates without error good sensitivity and efficiency.

The ability to measure energy of radiation and provide spectrographic information, discriminate between alpha and beta particles, and that large area detectors can be constructed.**Demerits:** expensive complex circuit.

That anode wires delicate and can lose efficiency in gas flow detectors due to deposition, the efficiency and operation affected by ingress of oxygen into fill gas, and measurement windows easily damaged in large area detectors.

Applications

- Commonly used in standards laboratories, health physics laboratories, and for physicsresearch.

- Seldom used in medical centers.

- The wire chamber is a multi-electrode form of proportional counter used as a researchtool.

- The proportionality between the energy of the charged particle travelling through thechamber and the total charge created makes proportional counters useful for chargedparticle spectroscopy.

- Proportional counters are also useful for high energy photon detection, such as gamma- rays, provided these can penetrate the entrance window. They are also used for the detection of X-rays to below 1 Kev energy levels, using thin walled tubes operating at oraround atmospheric pressure.

- These are used extensively to check for radioactive contamination on personnel, flat surfaces, tools and items of clothing.

c) Scintillator Counter:

Scintillator: a material that exhibits the property of luminescence on excitement by ionizing radiation. A scintillator detector is a combination of scintilla tor with an electric light sensor such as PMT or photodiode. PMT absorbs the light emitted by the scintillator and further re- emits in the form of electrons. The subsequent multiplication of those electrons result in an electrical pulse which on analysis provides information about incident radiation particles.

There are different scintillation materials avail such as sodium iodide, anthracene and naphthalene etc. A scintillator counter possesses many advantages such as resolution of gammarays for Co & Cs, linearity, density, speed, transparency and also manufacturing cost.
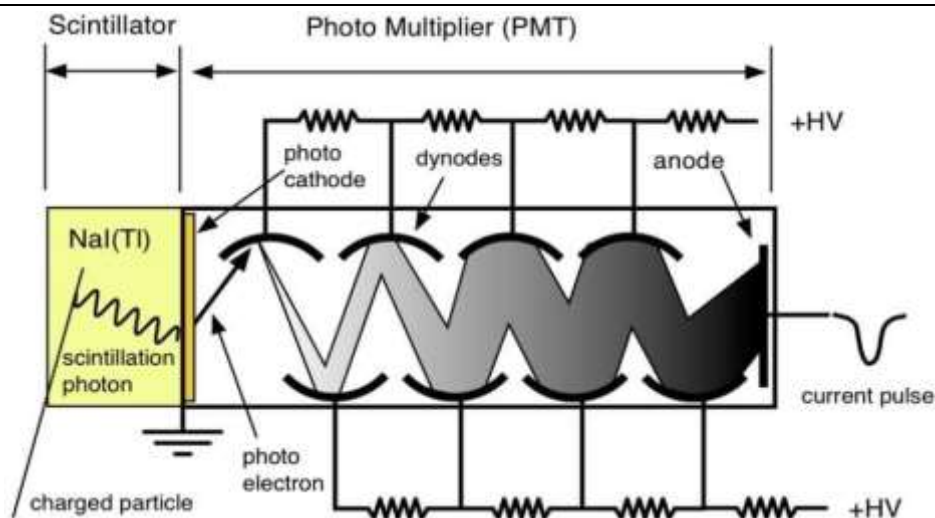
Fig 9: Scintillator Counter

d) Semiconductor Detector:-

These detectors assists in promotion of X-rays through generated electrons into conduction bands. Therefore the current so generated is a direct measurement of X-rays intensity. These semiconductor detectors commonly makes use of Indium antimonide or Lead telluride or Mercury cadmium telluride. In these detectors the thin layer of p-type of semiconductor is kept over the n-type surface to make a diffused p-n junction. The p-type surface is exposed to radiation w generates hole and electron pairs. These holes and electron pairs are separated by internal field existing on p-n junction. As a result voltage is generated. This assembly of semiconductor is arranged into a vacuum bottle cooling unit. The cooling is done through liquid nitrogen or Joule Thomson coolers of compressed nitrogen gas or liquid helium.
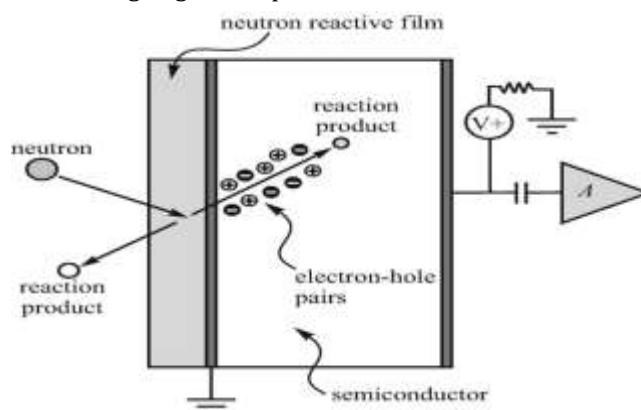
Fig 10: Semiconductor Detector

V.   DRUG PROFILE

Sr.no.	Properties	Ketoconazole
1	IUPAC Name	1-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan4-yl] methoxy] phenyl] piperazin-1-yl] ethenone
2	Appearance	Solid
3	Colour	White powder

4	Molecular formula	CHCINO
5	Molecular weight	531.4 g/mol
6	Melting point	148-152C
7	Log p	4.35
8	Category	Antifungal drug
9	Dissolution constant	4.3
10	BSC class	Class II (low solubility, high permeability)
11	Half life	2 -8 hours
12	Synonyms	Ketoconazol, Ketoconazole, Ketoconazolum, Ketozole
13	Bioavailability	Poor absorption by mouth (tab), negligible absorption through intact skin as topicalbioavailability is about 0.5 - 10%
14	Solubility	Freely soluble in DMSO, Soluble in methanol, dichloromethane, ethanol,insoluble in water. (In water, 0.29 mg/L at 20 °c)
15	Dose	200 mg taken once per dayfor up to 6 months.

Drug Structure:
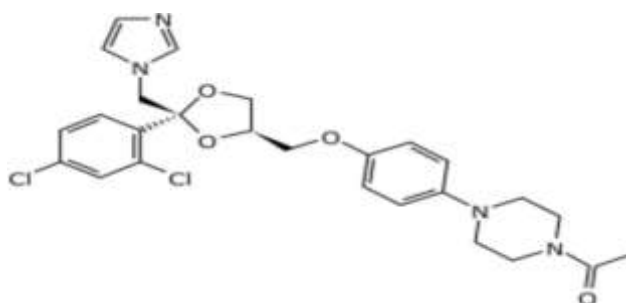
Fig 11: Ketoconazole

Background

Ketoconazole is an imidazole antifungal agent used in the prevention and treatment of a variety of fungal infections. Label It functions by preventing the synthesis of ergosterol, the fungal equivalent of cholesterol, thereby increasing membrane fluidity and preventing growth of the fungus.5,11 Ketoconazole was first approved in an oral formulation for systemic use by the FDA in 1981.9 At this time it was considered a significant improvement over previous antifungals, miconazole and clotrimazole, due to its broad spectrum and good absorption. However, it was discovered that ketoconazole produces frequent gastrointestinal side effects and dose-related hepatitis.9,10 These effects combined with waning efficacy led to its eventualreplacement by triazole agents, fluconazole, itraconazole, voriconazole, and posaconazole. Ketoconazole and its predecessor clotrimazole continue to be used in topical formulations. Ketoconazole is used in the treatment or prevention of fungal infections including blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis .Label In Europe, it is also used in the treatment of endogenous Cushing's syndrome.

Ketoconazole, similarly to other azole antifungals, is a fungistatic agentwhich causes growth arrest in fungal cells thereby preventing growth and spread of the fungusthroughout the body. Ketoconazole is approximately 84% bound to plasma albumin with another 15% associated with blood cells for a total of 99% binding within the plasma. Ketoconazole has an estimated volume of distribution of 25.41 L or 0.36 L/kg.5 It distributes widely among the tissues, reaching effective concentrations in the skin, tendons, tears, and saliva.6 Distribution to vaginal tissue produces concentrations 2.4 times lower than plasma. Penetration into the CNS, bone, and seminal fluid are minimal. Ketoconazole has been found to enter the breast milk and cross the placenta in animal studies.

Fig 12: Ketoconazole API PowderMechanism Of Action

Ketoconazole interacts with 14-α-sterol demethylase, a cytochrome P-450 enzyme necessary for the conversion of lanosterol to ergosterol. 5,11 This results in inhibition of ergosterol synthesis and increased fungal cellular permeability due to reduced amounts of ergosterol present in the fungal cell membrane. This metabolic inhibition also results in accumulation of 14α-methyl-3,6-diol, a toxic metabolite. The increase in membrane fluidity is also thought to produce impairment of membrane-bound enzyme systems as components become less closely packed.
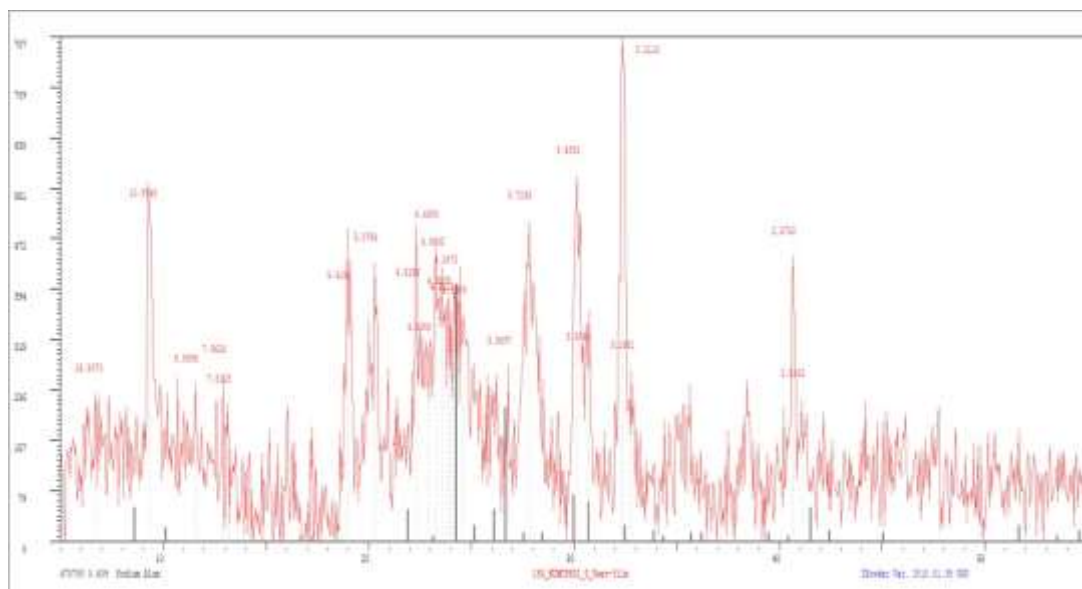
Graph:

Ketoconazole XRD Report

Fig 13:

Set-Fil	Phase name	Q	Fract	RIR.	% W Unc Ab	m/rho	% W Xtal	% W Xtal+A
862119	Cesium Sodium	1	1.000	1.10	48.4(3.1)	288.3	57.4(3.1)	38.9(2.1)
470708	Sodium Aluminum	1	0.970	1.00	51.6(3.3)	41.3	42.6(3.3)	28.8(2.2)
	Global amorphous	1	0.238	0.50	47.7(5.6)			32.3(4.0)

Fig 14:

Percentage Of Compounds Present

Compound	Chemical Formula	Crustal Shape
Cesium SodiumMolybdenum Cyanide Hydrate	C16 Cs7 H8.336 Mo2N16 Na O4.1	Tetragonal
Sodium AluminumSilicate Pentane 1,5-Bis(1,4-	C17 H34 N4 - Na - Al - Si - O - H2 O	Monoclinic

VI.　CONCLUSION

X-ray diffraction (XRD) is an analytical technique used to characterize crystalline phases of a wide variety of materials, typically for mineralogical analysis and identification of unknown materials. Powder diffraction data are fundamentally derived by the atomic and molecular arrangements explained by physics of crystallography.

In the past few years, powder XRD systems have become more and more efficient for the pharmaceutical industry due to innovations and improvements in detection and source emission technology. X-ray diffraction methods are especially significant for the analysis of solid materials in forensic science. They are often the only methods that allow a further differentiation of materials under laboratory conditions. Minerals are the building blocks of the solid Earth. Some minerals are readily recognized by their distinctive colors or crystal forms, but in most cases, powder X-ray diffraction is the primary and most definitive method used to identify minerals. The high flux and density of X-rays produced at synchrotrons provide the microelectronics industry with a powerful probe of the structure and behavior of a wide array of solid materials that are being developed for use in devices of the future. X-ray diffraction studies are also used to obtain information on the short and intermediate range structure of glasses.

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