CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2842261

Available online at: http://www.iajps.com *Review Article*

RIFAMPICIN: ANTI TUBERCULAR DRUG: AN OVERVIEW

[1]Nutan Shriram Bhoi, [1]Ms. Monika Ola*, [2]Mrs. Rajveer Bhaskar, [3]Nilesh Suresh Sathe, [4]Vaibhav Ghansham kute, [5]Rajeshwari satish patil

[1]Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur.

Article Received: March 2019 **Accepted:** April 2019 **Published:** May 2019

Abstract:

The World Health Organization inspires the use of fixed dose combination (FDC) of rifampicin combination used with isoniazid, isoniazid with pyrazinamide or pyrazinamide with ethambutol for the treatment of tuberculosis. Hence, it's used worldwide for reducing the risk of emerging drug resistance. Rifampicin is one of the potent and broad spectrum antibiotics against bacterial pathogen. It works by inhibits the DNA dependent RNA polymerase activity by forming stable complex with enzyme. Here, the polymorphic form of rifampicin is describe by thermal study of rifampicin. The thermal behavior of two polymorphic forms of rifampicin was studied by DSC, FTIR, TGA, PXRD. The thermoanalytical results clearly showed the differences between the two crystalline forms. Polymorph I was the most thermally stable form and polymorph II was meta stable. On the DSC study of rifampicin it was shows the difference between both form on basis of melting point and exothermic and endothermic peak. The DSC curve of form I RMP shows the exothermic peak at the temperature between 240- 420ºc and form II RMP shows the endothermic peak at temperature range between 183-188ºc. By using the FTIR spectrum of form I RMP, it was shown that the absorption bands at approximately 3400 cm^{-1}, 1722 cm^{-1}, 1643 cm^{-1}, for the OH of the chain loop group, acetyl group, furanone group sufficient to characterize form I of RMP and form II of RMP, it was shown that the absorption bands at 3356 cm^{-1} ,1732 cm^{-1}, 1714 cm^{-1}, for the OH group, furanone group and acetyl group are sufficient to differentiate form I and form II rifampicin. In TGA analysis of RMP both polymorphs shows TGA curve form I occurred at the temperature 224.17 ºC and form II showed the temperature at 194.04 ºC. Powder X-ray diffraction was used to test the polymorphic forms of solid-state rifampicin.

Keywords: *Rifampicin, thermal study, analytical study, multidrug resistance study, consequences.*

Corresponding author:

Ms. Monika Ola,

Assistant professor, Department of Pharmaceutics and QA
R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur
Karwand Naka, Shirpur, Dhule, Maharashtra, 425 405, India
Mobile No. 8275102108.Email id: monika.ola@rediffmail.com

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Please cite this article in press Monika Ola et al., ***Rifampicin: Anti Tubercular Drug: An Overview.,*** *Indo Am. J. P. Sci, 2019; 06(05).*

INTRODUCTION:

Tuberculosis is deadly infectious disease cause in the world today. An important thought in the treatment of tuberculosis is the reality that the aetiological agents, Mycobacterium tuberculosis (MBT) and mycobacterium avium complex have the capable to preserve intracellularly in the host macrophages for longer time period [1]. Actually, they are intracellular parasites that can grow firstly in macrophages, that can produce the efficacy of antimicrobial agents that are having a lower ability to penetrate into the phagocytic cells. In the treatment of tuberculosis the oral administration of rifampicin, isoniazid, ethambutol and pyrazinamide taken for a period of 6-12 months. These drugs are relatively toxic and cause several adverse effects. Moreover, drug resistance can occur when treatment is not followed to completion [2].

Currently the drug used in first line treatment of tuberculosis are rifampicin, isoniazid, ethambutol, streptomycin, pyrazinamide, fluoroquinolones and second line drugs are amikacin, cycloserine, capreomycin, cycloserine, kanamycin, ofloxacin, levofloxacin, para-amino-salicylic acid [1].

Who approved FDC drug for tuberculosis:

First line TB drugs**:** Isoniazid, rifampicin, pyrazinamide, ethambutol.

Second line TB drugs: Fluroquinolones, amikacin, cycloserine, capreomycin, cycloserine [3].

Table 1 : Fixed-dose combinations from the WHO Model List of medicine

Drug	Dose form	Strength for daily use	Strength for intermittent use 3 times per weak
Rifampicin + isoniazid(RH)	Tablet Tablet or pack of granules	150 mg + 75 mg 60 mg +30 mg	150mg +150mg 60mg+60mg
Ethambutol +isoniazid (EH)	Tablet	400 mg +150 mg	-
Isoniazid + thioacetazone (HT)	Tablet	100 mg + 50 mg 300 mg + 150 mg	-
Rifampicin + isoniazid + pyrazinamide	Tablet Tablet or pack of granules	150 mg + 75 mg + 400 mg 60 mg + 30 mg + 150 mg	150 mg + 150 mg + 500 mg -
Rifampicin + isoniazid + pyrazinamide + ethambutol (RHPE)	Tablet	150 mg + 75 mg + 400 mg + 275 mg	

RIFAMPICIN :

form Rifampicin is evaluate as the main constituent for the treatment of tuberculosis in concurrence with other first-line anti-TB drugs, which is being used both in the severe phase as well as in the maintenance of treatment. Rifampicin is a semisynthetic antibiotic-family of rifamycins, a rifamycin B derivative - create by strains of Nocardia mediterranei, discovered in the 1960s.

A rifampicin is geting from streptomyces mediterranei and it is a semisynthetic antibiotic It is a large spectrum of antibiotic, used antagonistic towards the some forms of mycobacterium [4]. It is sensitive to microorganisms which inhibits DNA- dependent RNA polymerase activity by forming a stable complex with the enzyme. It delay the evolution of RNA synthesis. Rifampicin has bactericidal effect and take action on both intracellular and extracellular organisms.

Rifampicin is a complex molecule shows the different formation due to interaction between their functional group, it has stimulating the different crystal morphologies. It exhibit red brown crystalline powder because of the dissimilar crystal morphologies and rifampicin shows polymorphism. It is existing two polymorphic form, form I and form II. Form I is stable and form II is meta stable. Besides these two polymorphic forms, RMP is found as hydrates (monohydrate, dihydrate and pentahydrate), as solvates and also in amorphous.

Table 2 : physical characteristics of rifampicin

Parameters	Result
Color	Red to orange platelets from acetone and red-brown crystalline powder
Molecular formula	$C_{43}H_{58}N_4O_{12}$
Molecular weight	822.94 g/mol
IUPAC name	5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadecane[1,11,13]trienimino)naptho[2,1-b]furan-1,11(2H)-dione21-acetate
Melting point	Polymorph I - 245- 260˚c Polymorph II - 183-188 °C
BCS class	Class II
Half life	3.35 hour
Protein binding	89 %
Water solubility	1400 mg/L
LogP	2.77
pKa	6.9 (Acidic) 7.53 (Basic)

STRUCTURE :

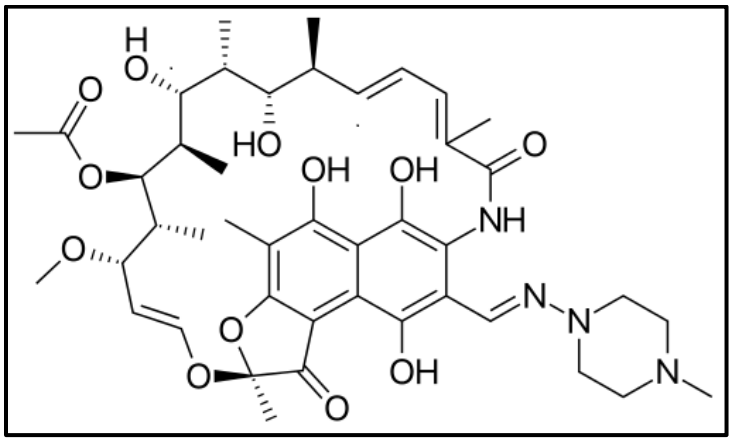

Fig. 1: Structure of Rifampicin [5,6]

Mechanism of action:
Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase[5,6]. Rifampicin binds to the pocket of the RNA polymerase β subunit within the DNA/RNA channel, but away from the active site [7,8,9].

Pharmacokinetic of rifampicin:
Absorption: Rifampicin go through quick and entire absorption after oral dose. Absorption is upgrade when the oral dose is taken on an empty stomach, as food may reduce the rate of absorption of rifampicin. Rifampicin absorption is especially responsive to changes in object formulation [10].

Distribution:
Rifampicin go through broad distribution into most body tissues and fluids, including the cerebrospinal fluid. It has a unique property of penetrating intracellularly. The protein binding is around 80%. Rifampicin was detected in maternal milk and it crosses the placenta [11]
.

Metabolism and Elimination:
Rifampicin is extensively eliminated by intestinal and hepatic metabolism and rapidly deacetylated. The drug and its metabolites are mostly eliminated in the bile and in stools. Rifampicin go through enterohepatic recirculation as its metabolites. At most a little amount

of the dose is eliminated in the urine 15-25 % providing the urine an orange color1 [12, 13].

Pharmacodynamic of rifampicin :
Rifampicin that inhibits DNA-dependent RNA polymerase action in liable cells because it have antibiotic action [11] . It attach with bacterial RNA polymerase but does not stop the mammalian enzyme. It has a wide spectrum of action opposed to gram-positive and gram-negative organisms which include Pseudomonas aeruginosa and Mycobacterium tuberculosis. Because of quick evolution of resistant bacteria. Its use is to restrict the treatment of mycobacterial infections and a small other sign [12]. Rifampin is absorbed when administered orally and it broadly distributed in body fluids and tissues. It metabolized in the liver [13].

Animal model use can use to study rifampicin:

1. Physiologically Based Pharmacokinetic model
2. Pharmacokinetic studies :
   A. Compartmental model
      I. Single or one compartmental model
      II. Multi Compartmental Model
   B. Non compartmental model
3. Animal study

Physiologically Based Pharmacokinetic model:
In vivo evaluation of TB drug used against is performed through the study of correlations between drug exposure and efficacy data, is carried out on experimental calculation of maximum concentration reach into blood circulation (Cmax) [14]. Then the system consider a pharmacology approach, modeling to describe efficiently determine in vivo response of anti- TB drug needed for preclinical response of drug. Necessary information of drug-drug and host drug bacterial interactions, for these system the mathematical model used for the drug therapy tested against TB drug in mice model [15]. In these model reproduce the exploratory studies and generate hypotheses with regard the efficacy of drug regimens that are not initially tested. Whereas biological approach to testing immune response of mycobacterium tuberculosis infection in both human and in mice [16].

The pharmacokinetic model test limited to human disease. Additionally, these PBPK models introduce little experimental data compared with other data obtained in animal models [17]. The mathematical tool required to support systems pharmacology framework for preclinical anti-tuberculosis drug evolution, we constructed whole body initial data of the in PBPK model of rifampicin. Now the treatment of TB requires the multiple drugs and mycobacterium tuberculosis is is potentially infect the tissue and whole body organs [18]. The pharmacokinetic model consist of rifampicin concentration in animal tissues and body fluids with various dose and routes of administration, were get from the details of rifampicin in other animals and humans were used for model evolution while the corresponding data are not available [19]. No distinction was made for measurement of rifampicin concentration in serum and plasma when data obtained from other models such as high performance liquid chromatography (HPLC) or bioassay.

Working of Physiologically Based Pharmacokinetic model (PBPK) ;
The Physiologically based pharmacokinetic model was based on entire body structure be composed of perfusion-restricted section parameterized by blood flow rates, tissue volumes and drug-based on tissue/blood partition coefficients.

After oral route of rifampicin was consisting as a pulsed input with 1st order absorption into the gut. Clearance of rifampicin through the kidney and liver. Clearance was describe in terms of total body clearance.

Enterokinase circulation was utilizing a one-compartment model for the gut lumen, with 1st order reabsorption into the gut and 1st order elimination in the feces. Blood flow and total clearance were based on three-fourth power of body weight. Model input consist of specified dosing regimen, set of parameter values and initial conditions of drug amount in every compartment. Model output consist of time dependent drug amount and concentration in blood and other tissues [19].

Consequences of improper dosing of rifampicin:
Rifampicin causes some times disturb stomach, heartburn, nausea, menstrual changes, drowsiness or dizziness.
Rifampicin may cause convert the color of urine, saliva or tears, sweat in orange to red brown. This effect is safe occured when medication is stopped. However, teeth and contact lenses may be cause permanent staining [20].

Rifampicin may causes significant liver disease. This is necessary to completely treat the certain infection cause by rifampicin and it has treat by combination of other drugs such as isoniazid, pyrazinamide it may grow this risk [20]. Rifampicin may causes severe

intestinal state due to the variety of resistant bacteria. This condition may often cause during the treatment or weeks to months when treatment has stopped.

Side effect of rifampicin :
Headache, yellow color of eyes or skin, nausea and vomiting, dizziness, loss of appetite, unusual behavior, muscle pain, skin rash, weakness and abdominal pain.

Drug resistance TB :
The infective bacteria that leads tuberculosis can produce resistance to the antimicrobial drugs used to treat the tuberculosis [20]. Multidrug-resistant TB that doesn't retort to isoniazid and rifampicin drug that are most potent anti-TB drugs. The two reasons why multidrug resistance tuberculosis endures to emerge and spread are misconduct of TB treatment and aerobic transmission. Almost all of people having TB are treated by a six month treatment that is providing to patients with support and observation. Unsuitable or incorrect use of antimicrobial drugs, or use of unproductive formulations and premature treatment disruption can cause drug resistance, which can be then transmitted, particularly in congested area such as prisons and hospitals [21].

Drug-resistant TB can occur when the drugs used to treat TB are misused or mismanaged. Examples of misuse or mismanagement include

- People do not complete a full course of TB treatment
- Health care providers prescribe the wrong treatment (the wrong dose or length of time)
- Drugs for proper treatment are not available
- Drugs are of poor quality

Type of drug resistant TB :
1. Multidrug-resistant TB (MDR TB)
2. Extensively drug- resistant TB (XDR TB)

Multidrug-resistant TB (MDR TB) :
Multidrug-resistant TB (MDR TB) is caused by TB bacteria that is resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease. TB experts should be consulted in the treatment of MDR TB.

Extensively drug- resistant TB :
Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Because XDR TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective.

XDR TB is of special concern for people with HIV infection or other conditions that can weaken the immune system. These people are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB [21]

TB experts should be consulted in the treatment of XDR TB.

Solutions to control drug-resistant TB are :
- Provide the proper treatment to TB patient in first time around.
- Provide the contact of TB patient to diagnosis.
- Confirm sufficient infection to control in facilities where patients are treated.
- Confirm the actual use of second-line drugs.

Stability of rifampicin:
Rifampicin should be stable at least minimum two years when it stored in desiccated -20°c and keep safe from light. Rifampicin is stable as a solidified at room temperature upto 70°c.

Storage condition of rifampicin:
- Avoid excessive heat (above 104º F)
- Protect from light
- Store at 77ºF; excursions permitted to 59-86ºF
- Use within 24 hours from time of preparation

Drug and food interaction:
Rifampin and Alcohol: Drinking alcohol while taking rifampin may increase your risk of liver damage.
Rifampin and Other Interactions: Rifampin may manufacture false-positive effect in urine screening tests for opiates. It can get involved with other laboratory tests, included in blood folate and vitamin B12 tests, liver and gallbladder function tests.

Identification of rifampicin :
pH : 4.5 to 6.5, determine in a 1.0 %w/v suspension [22]
Assay : Determine by liquid chromatography
Solvent mixture : A mixture of 10 volumes of 21.01 % w/v of citric acid, 23 volumes of a 13.61 %w/v solution of potassium dihydrogen phosphate, 77

volumes of a 17.42 % w/v solution of dipotassium hydrogen phosphate, 640 volumes of water and 250 volumes of acetonitrile.

Test solution: weigh quantity of powder containing 20 mg substance under the examination in 10 ml of acetonitrile, shake and filter. Dilute 5 ml of filtrate to 100 ml with the solvent mixture.

Reference solution: A solution containing 0.02 % w/v of rifampicin RS in acetonitrile and filter. Dilute 5 ml of this solution to 100ml with solvent mixture.

Chromatographic system: A stainless steel column 10 cm * 4.6 mm packed with octylsilane bonded to porous silica.

Mobile phase : A mixture of 65 volumes of a solution containing 0.1 % v/v orthopohosphoric acid, 0.19 % w/v sodium perchlorate, 0.59 % w/v of citric acid and 2.09 %w/v potassium dihydrogen phosphate and 35 volumes of acetonitrile,

Flow rate of column was 1.5 ml/min. spectrophotometer set at 254 nm and injection volume 20µl [22].

Inject the reference solution. The test is not valid unless the relative standard deviation for the replicate injections is not more than 2 %. Inject the reference solution and test solution. Calculate the content of rifampicin.

Loss on drying:

Not more than 1%, determine on 1 g by drying In an oven at 80º at a pressure not exceeding 0.7 kPa for 4 hours[22]

Thermal study of rifampicin polymorphs:
Rifampicin exist as a two form such as polymorph I and polymorph II. The polymorph I is most stable while polymorph II are meta stable. As well as these two principle form is found as hydrate and solvate, which change in amorphous form after removal of solvent.

Differential Scanning Calorimetry:
The DSC curves were getting on a DSC- 50 cell utilizing aluminium crucibles with 2 mg weight of sample, under the dynamic N2 atmosphere with the rate of 50 mL min^{-1} and heating rate of 10°C min^{-1} between 25 to 500°C.

The thermal measures observed on the DSC curve according to mass losses showed on TG/DTG/DSC curves. The DSC curve showed an endothermic peak with heat variation starting at 183 - 188ºC. The endothermic peak which occurred at 184.69ºC is the characteristics of a melting process followed by recrystallization, which is later characterized by exothermic peak starting at 245 - 420°C. The exothermic peak which occurred at 245.29 °C having melting point[23]. The thermal decomposition process peak started with heat liberated from recrystallization which make polymorph I and continued exothermally.

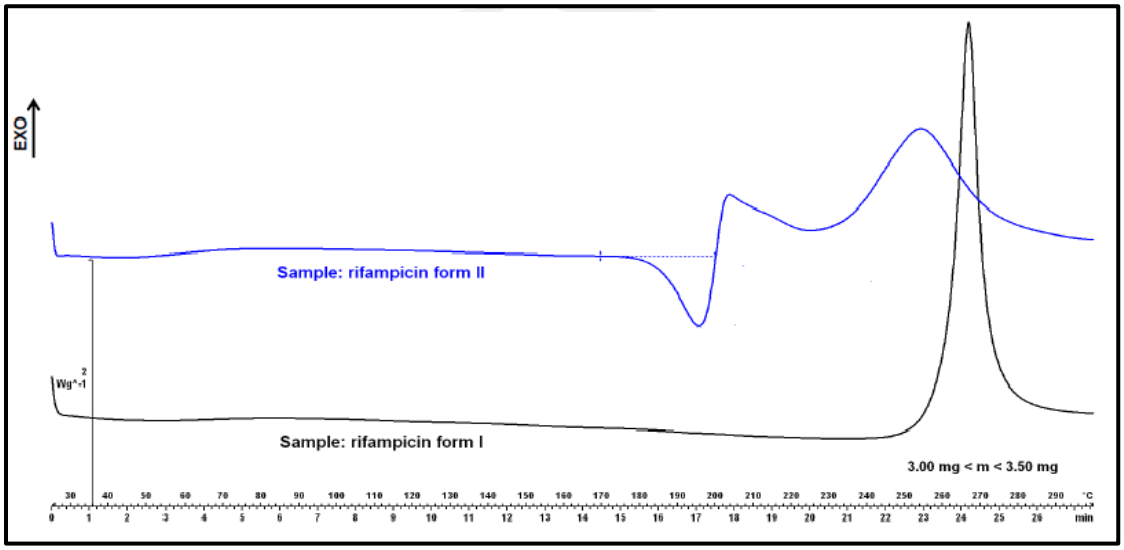

Fig 2: DSC thermogram of Rifampicin polymorph I and polymorph II [23]

Fourier transform infrared spectroscopy (FTIR) of polymorph I and polymorph II :

FTIR spectrum of form I of Rifampicin, getting with a resolution of 4 cm−1 in the region 4000-650 cm−1, where the major absorption bands characterizing this drug are detected[23,24]. The dissimilar crystal packing of rifampicin, assign to the different possibilities of hydrogen bonding, conformational exchanges, and ionization states, is the clearest evidence of its polymorphism. All the functional class that can be include in H bonding are intra molecularly bonded, also confirmed by our X-ray analysis, acetyl group, be visible differences in OH of the chain loop, furanone group and amide C=O frequencies. Such differences are main to distinguish polymorphic forms of rifampicin.

In Fig.3 shows the ranges of both polymorphs.

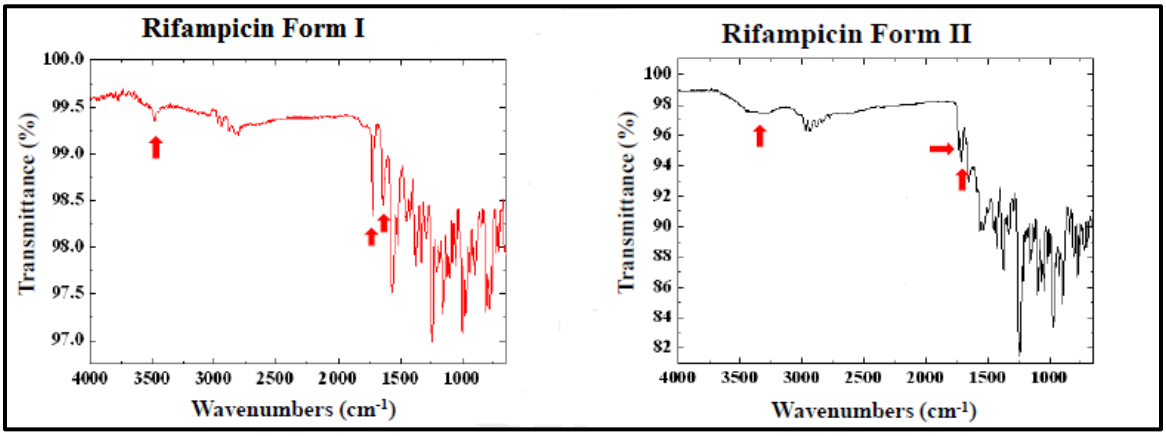

Fig 3 FTIR Spectra of polymorph I and polymorph II [23, 24]

Table 3 : FTIR spectra of rifampicin form I

Standard peak cm^{-1}	Observed peak cm^{-1}	Functional group
3400-3200	3400	Ansa OH
1725-1700	1722	Acetyl C=O
1680-1630	1643	Furanone C=O

Table 4 : FTIR spectra of rifampicin form II

Standard peak cm^{-1}	Observed peak cm^{-1}	Functional group
3400-3200	3356	Ansa OH
1750-1730	1732	Furanone C=O
1725-1700	1714	Acetyl C=O

Thermogravimetric Analysis (TGA):

Thermogravimetric analysis (TGA) (Mettler-Toledo, Greifensee, Switzerland) was applied to get the weight forgetting and breaking up temperature of polymorphs. TGA curve were present with on 851e Mettler Toledo with heating rate10°C/min and atmosphere of N2 flow rate: 50mL/min. The equipment was calibrated with indium and aluminum [25,26].

The rifampicin polymorphs were examined from 298.15 to 573.15 K at heating rate of 10 K/min below the defence of nitrogen gas[27]. In TGA analysis, no weight forgetting upto 190ºC has specified the absence of either solvate or hydrate in standard as well as trade samples. In the graph of TGA curve form I occurred at the themperature 224.17 ºC and form II showed the temperature at 194.04 ºC

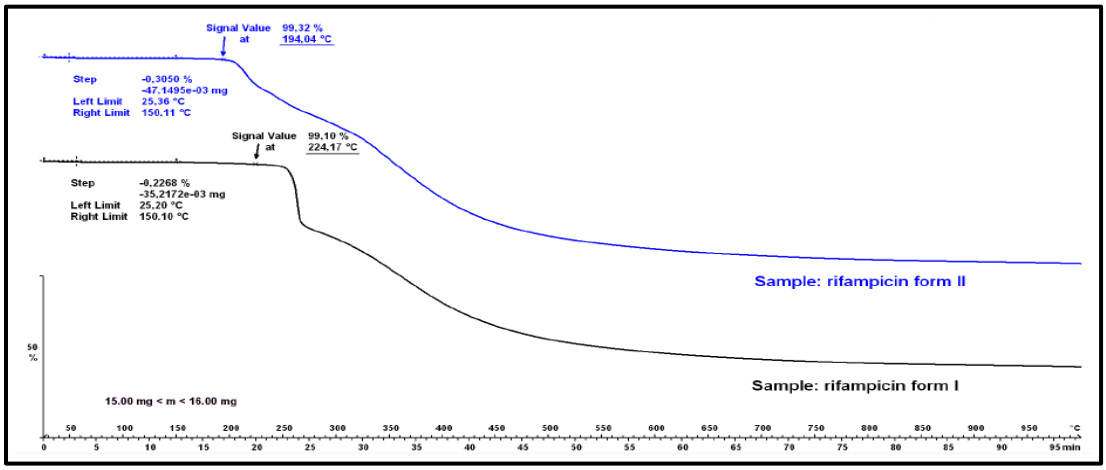

Fig 4 : Thermogravimetric analysis of polymorph I and polymorph II[25, 26]

Powder X-Ray Diffraction :

Powder X-ray diffraction (PXRD) was used to test the polymorphic forms of solid-state rifampicin. The details were obtained on Rigaku D/ max-2500 (Rigaku, Japan) utilizing Cu-Ka radiation (0.15405 nm) with electric current of 100 mA, and voltage of 40 kV. The samples were inspect above diffraction angle (2q) from 2 to 30 at step size of 0.02 and scanning rate of 8 min^{-1}.

Polymorphic forms I and II were readily detectable from their p-XRD patterns which are shown in Fig 5. The characteristic peaks for form I were seen at 13.65 and 14.35º 2θ, whereas form II present at 9.93 and 11.10º 2θ [27].

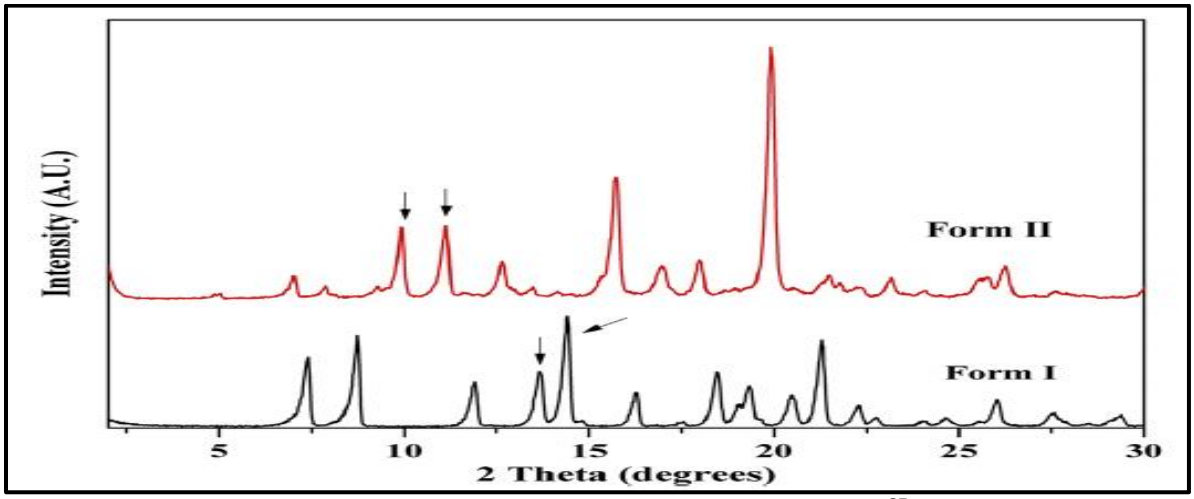

Fig 5. : PXRD Spectra of polymorph I and polymorph II [27]

Analytical method of rifampicin :

Thin layer chromatography:

TLC has been used in field of rifampicin and colored spots are directly located. Many TLC procedure were developed for analysis of rifampicin and it's metabolites body fluids. The RF values were shown to be dependent on the concentration. The spots were quantitiated by using the bioautographic technique, densitometric, visual estimation or by the elution method by microbiological aasay. A stationary phase partition TLC procedure has been describe for the determination of rifampicin. Silica gel plates were used as stationary phase, phosphate buffer pH 7 containing 0.1% sodium ascorbate as mobile phase.

The colored spot was eluted and measured spectrometrically [28]

Column chromatography :
The content of rifampicin and it's metabolites in urine, bile and serum was determine by extraction with chloroform and by column chromatography followed by spectrophotometry. The liquid- solid chromatography was carried out using glass column 7 cm long, 4 mm internal diameter, packed with silica gel G, buffered at pH 6 and chloroform and chloroform- methanol in pregressively increasing amount as solvent, at a flow rate of 0.15 ml/min. Rifampicin and its metabolites were quantified by reading the absorbance of the eluates at specific wavelength [28]

Paper chromatography :
A paper chromatographic technique for determination of rifampicin and 25- deacetylrifampicin was used foe urine and bile. Was carried out on whatman 3mm paper using methanol : n- octanol as stationary phase and aqueous buffer, pH 6, as mobile phase for hours. The intensity of the red-orange spots was measured by an analytrok photodensitometer or material determined bioautographically. Paper chromatographic method for the separation of rifampicin and its metabolites using ethyl acetate-water- dimethylformamide (10:10:1) [28]

High pressure liquid chromatography :
Drug content and dissolution samples were analysed using an HPLC system with UV detection. Chromatography was performed using a Bondapak C18 10 mm 3.9 ¥ 300 mm column (Waters) and a SecurityGuard guard column. The mobile phase, consisting of methanol–acetonitrile-phosphate buffer solution (pH 5.2), 50:17:33, was eluted at a flow rate of 1.2 ml/min, and the UV detector was set to drug wavelength. The column temperature was maintained at 25°C and the volume of each sample injected was 50 ml[2]

Marketed formulation :

Formulations	Dosage forms	Manufacturer
Rifampicin 150 mg	Tablet	Hetero healthcare PVT LTD
Rifampicin 450 mg	Capsule	Lupin LTD
Rifacip 150 mg	Capsule	Cipla Ltd
Rifampin 600mg/ 10ml	Injection, lyophilized powder	Akorn LTD
Tibrif 450 mg	Tablet	Agron remedies PVT. LTD
Rimpin 150 mg	Capsule	Hetero healthcare LTD
Rimactane 200 ml	Syrup	Novartis INDIA LTD
Rifit 200ml	Syrup	Finecure pharmaceuticals
Rifalone 450 mg	Tablet	Medispan LTD
Rifampicin 300 mg	Capsule	Lupin LTD
Monocin 600 mg	Tablet	Overseas healthcare PVT LTD
Rifalite 450 mg	Capsule	Elite pharma PVT LTD
Rifit 650 mg	Tablet	Finecure pharmaceuticals
Rifampicin (300 mg) + isoniazid (150 mg)	Capsule	Sanofi- Aventis
Rifampicin(120 mg) + isoniazid (50 mg)+ pyrazinamide(300 mg)	Tablet	Remedy repack
Rifampicin (300mg) + Isoniazid (50 mg) + Pyrazinamide (120 mg)	Tablet	Sanofi- Aventis
Rifampicin 300 mg + Isoniazid 150 mg	Capsule	Sanofi- Aventis

Routes of administration, dose and Effectiveness of rifampicin :

Dose	Routs of administration	Effectiveness
600 mg (adult)	Oral administration	Peak serum concentration was 32 mcg/ml
300 mg (adult)	IV administration	Mean plasma concentration of rifampicin upto 8 hr was 1.1±0.6 mcg/ml
600 mg (adult)	IV administration	Mean plasma concentration of rifampicin upto 12 hr was 1.2±0.6 mcg/ml
10 mg/kg body weight (pediatric)	Oral administration	mean peak serum concentrations of 3.5 mcg/mL
10 mg/kg body weight (pediatric)	IV administration	mean peak serum concentration of rifampin at the end of a 30-minute was 25.9±1.3 mcg/mL

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