PQM Promoting the Quality of Medicines

PRODUCT INFORMATION REPORT

RIFAPENTINE

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About PQM

The Promoting the Quality of Medicines (PQM) program is a cooperative agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). The PQM program provides technical assistance to strengthen medicines regulatory authorities and quality assurance systems and supports manufacturing of quality-assured priority essential medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal and child health.

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Executive Summary

Rifapentine was first synthesized in 1965. The drug was approved by the Food and Drug Administration (FDA) in June 1998 (NDA # N021024), for the treatment of pulmonary tuberculosis (TB) in combination with one or more antituberculosis drugs. It is currently marketed under the brand name Priftin® by Sanofi in the United States. There are no unexpired patents or exclusivity for this product in the US FDA's "Orange Book" database.[2]

This product information report summarizes the available literature and provides expert scientific analysis of the physicochemical, biopharmaceutics and toxicological properties, API synthesis, analytical, formulation, and manufacturing of rifapentine. The authors have taken great care to appropriately cite all references used in this report and provide proper attribution where necessary. It is expected that the PIR will provide critical information and guidance to manufacturers, as well as stakeholders concerned with access and supply of priority essential medicines.

The following information is provided: chemical structure/formula, IUPAC Name, physico-chemical properties, moisture sorption, and solubility related data of the rifapentine. Rifapentine has been characterized through various techniques such as FTIR, NMR, XRD, MASS, UV VISIBLE, and has been summarized in the document. Rifamycin S is the starting material for the synthesis of rifapentine. Different synthetic routes and their mechanism to synthesize rifapentine are also discussed. This PIR also highlights the stability in aqueous and dry states and gives the mechanism of degradation and the degradation products formed. Rifapentine has been reported to exist in different solid forms (US patent 4,002,752), including solvates and amorphous forms. However, a polymorphic form of the drug substance used in Priftin® is not available.

Rifapentine is a red-colored dye. It is recommended to protect rifapentine from high humidity and temperatures. Although the calculated Permitted Daily Exposure (PDE) value is > 10µg/day, a dedicated manufacturing facility for both API and SDF is recommended in light of the dye nature of rifapentine. The qualitative formula for the leading marketed formulation, Priftin®, is described with proposed functions of the excipients along with US FDA IID limits for the individual excipient.

Acute toxicity values published include oral LD_{50} in mice of 2000 mg/kg and in rats of 1700 mg/kg. Rifapentine is not listed as a known human carcinogen in any groups of

the International Agency for Research on Cancer (IARC). Rifapentine is an FDA pregnancy category C drug. The values calculated for Occupational Exposure Limit (OEL) and Acceptable Daily Exposure (ADE) of rifapentine were 125 μg/m^3 and 1 mg/day respectively. Based on the OEL value, rifapentine falls in Category 2 (100-1000 μg/m^3) of the 4-band control banding system. However, the safety data sheet (SDS) from Sigma-Aldrich lists rifapentine as belonging to Category 3 [4]. Safe handling precautions include avoiding contact with skin and eyes. Additionally, formation of dust and aerosols should be avoided. Adequate general or local exhaust ventilation should be provided to keep airborne concentrations below the permissible exposure limits. In order to avoid exposure to the risks of rifapentine contamination and to lower risks of good manufacturing practices (GMP) non-compliance issues during the manufacturing of the active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP), dedicated and self-contained facilities with adequate AHU and HEPA filters are the recommended control mechanism wherever the product is exposed to the environment. Normal measures should be taken for fire prevention protection. Because of eye, skin, and breathing irritation proper protective personnel equipment (PPE) such as gloves, clothing, and breathing masks is recommended for processing operators [4, 7]. For nuisance exposure use type P95 (US) or type P1 (EU EN 143) particle respirator. For higher level protection use type OV/AG/P99 (US) or type ABEK-P2 (EU EN 143) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Key Manufacturing Challenges

The table below summarizes the key challenges associated with the manufacture of rifapentine.

Challenges	Description of the challenges and solution
Inherent properties	Rifapentine is a red-colored dye by nature which inherently makes cleaning and cleaning validation necessary to demonstrate the control of cross-contamination very difficult. As such the product needs to be manufactured using dedicated equipment and rooms. This can present a significant financial, technical, and operational challenge for manufacturers. Similar challenges exist with rifampicin which requires manufacturers to have segregated manufacturing operations. Refer to section on Formulation Barriers to Entry and Process Equipment Selection for additional discussion.
Product development (formulation and analytical)	Rifapentine used in combination with other TB products such as INH present technical challenges. Chemical interaction between rifapentine and INH to form isonicotynl hydrazine is a challenge in developing and manufacturing this product.The acidic nature of INH and other amino acid-containing excipient further accelerates decomposition of rifapentine through Maillard reaction. Thus, rifapentine drug substance should not be directly exposed to acidic environment and amino-containing excipients. Selection of neutral excipients or other antioxidants to improve the stability of Rif/INH formulation can however be challenging. Spray-coating, granulation of the active, or use of bilayer tablet are possible solutions but very challenging for generic manufacturers due to cost and technical know-how required. Finally, method development and validation to enable proper characterization of the isonicotynl hydrazine impurity can also be challenging. Refer to the section on Formulation Challenges for additional discussion.
Product development (quality specification)	There are no specific monographs for rifapentine API and FPP. There are no quality-assured suppliers of rifapentine API for the public health market and no approved generic sources. It has proven difficult for generic manufacturers to establish their own validated method to characterize the drug substance and impurities.

Challenges	Description of the challenges and solution
Bioequivalence and biowaiver	There is no specific guidance on the requirements of rifapentine BE and DS profile study design both from EMA, US FDA, and WHO Prequalification Team. The BCS categorization is also not available. The manufacturers need to conduct the BCS characterization (e.g. solubility and permeability studies) and develop a dissolution profile both for quality monitoring and to demonstrate comparative dissolution with the referenced product. Refer to the section on Bioavailability and Pharmacokinetics for additional discussion.

Solid Dosage Form

General Summary

Rifapentine is an antitubercular agent used in the treatment of pulmonary tuberculosis. It was approved by FDA in 1998 and is currently marketed under the brand name of Priftin® by Sanofi in the US [5]. A supplementary new drug application was approved by FDA in November 2014 for its use in latent tuberculosis infection (LTBI) along with Isoniazid (INH) in patients 2 years of age or older, with high chances of tuberculosis infection [4]. The current manufacturer for rifapentine active ingredient is Sanofi-Aventis S.p.A., Zona e Punto Franco, Casella Postale 199, Brindisi, Italy. Priftin® film-coated tablet is currently manufactured by Sanofi-Aventis S.p.A., Località Valcanello, 03012 Anagni, Italy [6]. In December 2011, CDC recommended the use of 3 rifapentine/INH as an effective alternative regimen for the treatment of LTBI in patients' ≥12 years old in the US [36]. In November 2014, FDA approved a supplemental new drug application for rifapentine for the treatment of LTBI in combination with INH in patients 2 years of age and older at high risk of progression to TB disease. The current manufacturers for rifapentine active ingredient are Sanofi-Aventis S.p.A. and Zona ex Punto Franco, Casella Postale 199, Brindisi, Italy. There are no DMFs filed for the rifapentine API as of October 2, 2017.

FDA review for Priftin® reported a pharmacodynamics study where rifapentine given twice a week provided comparable results to a daily dose of rifampicin. Hence, rifapentine can be considered more potent than rifampicin [8].

Formulation Barriers to Entry

Cross Contamination

Rifapentine is a red-orange colored compound. Its administration is reported to cause discoloration of human excreta and eyes [7]. Because it is a red-orange dye, it is very difficult to clean the manufacturing equipment. Therefore, dedicated manufacturing equipment and processing areas for rifapentine are recommended.

Toxicity

Rifapentine is reported to cause hepatotoxicity. However, the effects caused by rifapentine on the liver are not well-defined and are likely similar to rifampicin. Because

antituberculosis multidrug treatments, including the rifamycin class, are associated with serious hepatic events, patients with abnormal liver tests and/or liver disease should only be given rifapentine in cases of necessity and with caution under strict medical supervision. Long-term therapy with rifapentine is associated with minor but fleeting elevations in serum aminotransferase levels in 2-7% of patients. If signs of liver disease occur or worsen, rifapentine should be discontinued. Rifapentine is usually given in combination with INH and/or pyrazinamide (well-known hepatotoxic agents). Therefore, the cause of acute liver injury in patients on rifapentine containing regimens becomes difficult to relate to a single agent. However, evidence suggests that these combinations were more likely to cause liver injury than the individual drugs [5].

Hepatotoxicity of other antituberculosis drugs (e.g., isoniazid, pyrazinamide) used in combination with rifapentine should also be taken into account. Competition between the related drug rifampin and bilirubin can occur. Therefore, hyperbilirubinemia resulting from competition for excretory pathways between rifapentine and bilirubin cannot be excluded. Rifapentine is likely to produce a predominately red-orange discoloration of body tissues and/or fluids (e.g., skin, teeth, tongue, urine, faeces, saliva, sputum, tears, sweat, and cerebrospinal fluid). Contact lenses or dentures may become permanently stained. Rifampin has enzyme-inducing properties, including the induction of delta amino levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampin administration. Based on these isolated reports with rifampin, it is assumed that rifapentine has a similar effect.

Hypersensitivity reactions may occur in patients receiving rifapentine. Signs and symptoms of these reactions may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). There have been reports of anaphylaxis. Reported gastrointestinal side effects include nausea, diarrhoea, vomiting, abdominal pain constipation, dry mouth, dyspepsia, oesophageal irritation, gastritis, and pancreatitis.

Rifapentine combined with other antituberculosis drugs has also been associated with anaemia, lymphopenia, neutropenia, and thrombocytosis.

Rifapentine is mostly absorbed orally achieving peak concentrations in 5 hours (approx.), with 60-70% oral bioavailability and 97-98% bound to plasma proteins. The half-life of rifapentine is 13.2 hours and approximately 70% of an orally administered dose of rifapentine is excreted in the faeces and 17% in the urine. It is reported that greater than 80% of the total rifapentine dose was excreted from the body within 7 days. Half of experimental animals are estimated to die with an oral dosage that is >65

times and >110 times than the human dose for antibacterial use (600 mg/kg) in mice and rats respectively. Published acute toxicity values include oral $LD_{50}S$ in mice of 2000 mg/kg and in rats of 1700 mg/kg.[5, 7, 9, 10]

There is no experience with the treatment for acute overdose of rifapentine at doses exceeding 1200 mg per dose. Clinical experience with rifampins suggests that within a few hours of overdose, gastric lavage to evacuate gastric contents followed by instillation of an activated charcoal slurry into the stomach, may help adsorb any remaining drug from the gastrointestinal tract.

Rifapentine and 25-desacetyl rifapentine are 97-98% and 93.2% plasma protein bound, respectively. Rifapentine and related compounds excreted in urine account for only 17% of the administered dose. Therefore, neither haemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifapentine from the body of a patient with rifapentine overdose[2, 7].[5, 7, 9, 10]

Carcinogenic, reproductive, and developmental hazards

Hepatocellular carcinomas were increased in male NMRI mice which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5th of the recommended human dose, in the intensive phase, based on body surface area conversions). In a two year rat study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, based on body surface area conversions) [2, 5, 7].

Rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria (Ames test); in vitro point mutation test in *Aspergillus nidulans*; in vitro gene conversion assay in Saccharomyces cerevisiae; host-mediated (mouse) gene conversion assay with Saccharomyces cerevisiae; in vitro Chinese hamster ovary cell/hypoxanthine-guaninephosphoribosyl transferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.

25-desacetyl metabolite of rifapentine was positive in the in vitro mammalian chromosome aberration test in V79 Chinese Hamster cells. 25-desacetyl metabolite of rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria (Ames test), the in vitro Chinese hamster ovary cell/hypoxanthine-guaninephosphoribosyl transferase (CHO/HGPRT) forward mutation assay, and the in vivo mouse bone marrow micronucleus assay [2, 5, 7].

Rifapentine is not listed as a known human carcinogen in any groups of IARC [2, 5, 7]. Rifapentine is an FDA pregnancy category C drug. There are no adequate and well controlled trials of rifapentine in pregnant women. However, a limited number of clinical trials for various Priftin® (rifapentine) treatment regimens for active tuberculosis and latent tuberculosis infection have pregnancy outcome data. The reported rate of spontaneous abortion following Priftin® exposure did not represent an increase compared to the rate of spontaneous abortion reported in the general population. Further interpretation of these data is limited by the quality of clinical trial adverse event reporting.

In animal reproduction and developmental toxicity studies, rifapentine produced foetal harm and was teratogenic at doses less than and similar to the recommended human dose. Because animal studies are not always predictive of human response, rifapentine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus [2, 5, 7].

Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to 20 mg/kg/day (one-third of the human dose based on body surface area conversions) [2, 5, 7].

It is not known whether rifapentine is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother and the benefits of breastfeeding. Since rifapentine may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk.

A slight increase in rat pup mortality was observed during lactation when dams were dosed late in gestation through lactation [5].

OEL calculations

Utilizing the NOAEL [5] and uncertainty/safety factor for determining occupational exposure limits as presented by Robert [2, 11], and considering uncertainty factors discussed by Naumann and Weideman [12], an occupational exposure limit for rifapentine can be calculated as follows:

OEL = NOAEL (mg/kg/day) x BW (kg) / V (m^3/day) x S x UF x MF x α

OEL = 80 mg/kg/day x 70 kg / 10 m^3/day x 10 x 90 x 1 x 5 = 0.125 mg/m^3 = 125 µg/m^3

NOAEL = no observable adverse effect level

UF = uncertainty factors (3 for monkey to human extrapolation, 10 for inter-human variation, 3 for reproductive effects in animals)

MF = modifying factor of 1 (default).

S = steady state based on elimination half-life = 10

α = pharmacokinetic factor based on bioavailability = 5

V = volume of air breathed in a shift = 10 m^3

This OEL is designed to be an 8-hour a day, 40-hour a week airborne concentration which nearly all workers may be repeatedly exposed to day-after-day without adverse health effects, based on currently available information. It does not take into account hyper-sensitive or otherwise unusually responsive individuals or persons with rifapentine hypersensitivity, which may be exacerbated by exposure to this drug.

Control band assignment

Rifapentine has been assigned as Category 2 (100-1000 µg/m^3) substance in the 4-band control banding system[13].

Table 1. Band system for hazardous chemicals

Band No	Target Range of Exposure Concentration	Hazard Group	Control
1	>1 to 10 mg/m^3 dust >50 to 500 ppm vapor	Skin and eye irritation	Use good industrial hygiene practice and general ventilation
2	>0.1 to 1 mg/m^3 dust >5 to 50 ppm vapor	Harmful on single exposure	Use local exhaust ventilation
3	>0.01 to 0.1 mg/m^3 dust >0.5 to 5 ppm vapor	Severely irritating and corrosive	Enclose the process
4	<0.01 mg/m^3 dust <0.5 ppm vapour	Very toxic in single exposure, reproductive hazard, sensitizer	Seek expert advice

Industrial hygiene sampling and analytical methods

Precautions for safe handling:

- Avoid contact with skin and eyes
- Avoid formation of dust and aerosols
- Use adequate general or local exhaust ventilation to keep airborne concentrations below the permissible exposure limits
- Normal measures for preventive fire protection

Analytic laboratory methods:

- Method is applicable to rifapentine
- Method involves reaction with 0.1N HCl producing stable products having λ_{max} 478 nm
- Concentrations as low as 5 µg/mL were detected [14]

ADE calculations

Utilizing the uncertainty/modifying factor method for determining Acceptable Daily Exposure (ADE) values with consideration to the methods discussed by Sergant, et al. [15] and the European Medicines Agency [16], an ADE for rifapentine can be calculated as follows:

ADE = (POD mg/day) / UF_C x MF x PK

ADE = 600 mg / 30 x 5 x 4 = 1 mg/day

Where:

POD = Point of Departure

BW = Body-weight (kg)

UF_C = (UF_A x UF_H x UF_S x UF_E x UF_R)

UF_A = Interspecies

UF_H = Intraspecies variability

UF_S = Length of study

UF_E = Severity of effect

UF_R = Reference effect level

MF = Modifying Factor

PK = Pharmacokinetic Factor

The ADE is the daily dose of a substance, below which no adverse effects are anticipated by any route, even if the exposure occurs over a lifetime.

Choice of uncertainty and modifying factors

In calculating the ADE value for rifapentine, a composite UF_C of 60 was used. The choice was made to account for the following factors:

1. The lowest daily therapeutic dose (600 mg) was selected as the point of departure. A factor of 1 was applied to UF_A because this dose is based on human data.
2. In the absence of specific intraspecies variability of data, a conservative default factor of 10 is applied to UF_H to extrapolate from general human population to sensitive subgroups, such as children and geriatrics [17].
3. The data reviewed was based on a one year study; therefore, an uncertainty factor of 1 was applied to UF_S [5].
4. Based on market data, the adverse health effects are moderate. A considerable number of people have experienced hepatotoxicity and hypersensitive reactions due to rifapentine; therefore, an uncertainty factor of 3 was applied to UF_E.
5. A minimum daily therapeutic dose has been established; and an uncertainty factor of 10 was already applied in UF_H to protect sensitive subgroups, therefore, an uncertainty factor of 1 was applied to UF_R.
6. The database of information was complete; therefore, a modifying factor of 5 was used to account for adverse effects other than hepatotoxicity and hypersensitivity and for extensive protein binding of rifapentine and its metabolite [5].
7. A composite PK factor of 4 was used to account for variable human pharmacokinetics [5].

Sensitizing Compound and Cross Contamination

Rifapentine has been reported to cause a rifamycin-induced hypersensitivity reaction in the sensitive patients. Permissible Daily Exposure (PDE) calculated from OEL was 1250 µg/day. According to the recent publication of Questions and Answers by European Medicines Agency (EMA), 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' (EMA/CHMP/CVMP/SWP/169430/2012), Rifapentine is a non-hazardous compound [18], because the calculated PDE value is > 10 µg/day. However, this is a generalized guidance stand-alone document, and other safety and toxicity aspects have to be considered for a more holistic approach. Additionally, the Safety Data Sheet (SDS)

published by Sigma –Aldrich categorized it as category 3 for lung exposure and PPEs are recommended for protection [4]. Rifapentine is also associated with hypersensitivity reactions: 5% of rifapentine exposed patients suffered from hypersensitivity reactions [5]. Based on overall literature available, it is recommended to have a dedicated manufacturing facility for rifapentine API and SDF.

Reverse Engineering

A qualitative formula for the leading marketed formulation was retrieved from the FDA review document of Priftin® NDA. Priftin® for oral administration contained 150mg per tablet of the active ingredient rifapentine [2].

For a manufacturer developing a generic version of the SDF, it is recommended to generate the necessary data by conducting appropriate tests on the reference listed drug (RLD) samples. Qualitative composition is generally available in the literature. Attempts should be made to determine the quantitative composition of at least the key functional excipients, and the amount which can affect drug product performance. Bansal, A.K, & Koradia. V. (2005) suggest reverse engineering through decoding of RLD's quantitative formula by identifying which excipients most affect product performance and quality (e.g., dissolution, stability or manufacturability). RLD decoding and reverse engineering information is important to shorten the intensive traditional trial and error formulation optimization techniques. In general, pH-adjusting agents, buffers, stabilizers (e.g., antioxidants and chelating agents), and dissolution modifiers (e.g., surface-active agents) are the best candidates for reverse engineering decoding experiments [19].

Discussion of Excipients

A list of excipients with their proposed function in a Priftin® tablet is provided in Table 2 [10]. Priftin® is a film-coated tablet. FDA's Inactive Ingredient Database (IID) can be accessed for individual inactive ingredient tablets [20], which provides the dosage forms the excipient is approved for and the maximum concentration approved for that dosage form. Quantitative limits for excipients were checked for oral film coated tablets in the IID and other references [9, 20, 21]. A generic product manufacturer is recommended to use the same inactive ingredients in concentrations that not exceed the maximum concentrations provided in Table 2.

Table 2. List of Inactive Ingredients with Their Proposed Function and IID limits

Ingredient	Function	Reference (Pages of Reference)	IID Limit for oral tablet [20]	Usual recommended concentration
Calcium stearate	Lubricant	[21] pp. 103-04	16 mg	Up to 1%
Disodium EDTA	Chelating agent	[21] pp. 242-44	4 mg	0.005-0.1 %
FD&C blue No. 2 aluminium lake	Coloring agent	[9]	1.81 mg	-
Hydroxypropyl cellulose	Tablet binder or coating agent	[21] pp. 317-24	187.6 mg	2-6 %
Hypromellose USP	Tablet binder or coating agent	[21] pp. 326-29	536.8 mg	2-5 % (binder): 2-20 % (coating)
Microcrystalline cellulose	Binder/diluent/adsorbent (@20-90% Concentration), antiadherent/disintegrant (@5-20% concentration)	[21] pp. 129-33	665.3 mg	20-90 % (diluent): 5-20 % (disintegrant)
Polyethylene glycol	As film coating or polishing material in film coating	[21] pp. 517-22	20 mg (PEG 400); 44 mg (PEG 6000)	5-30 %
Pregelatinized starch	Diluent (up to 75%), as binder in dry granulation (up to 20%), binder in wet granulation as well as disintegrant (up to 10%)	[21] pp. 691-94	240 mg	Up to 75% (diluent); up to 10% (disintegrant or binder)
Propylene glycol	Plasticizer in film coating	[21] pp. 592-94	14.4 mg	10-25% (oral solutions)
Sodium ascorbate	Antioxidant	[21] pp. 625-27	5 mg	-
Sodium lauryl sulfate	Wetting agent and/or tablet lubricant (@1-2%)	[21] pp. 651-53	15 mg	1-2 %

Ingredient	Function	Reference (Pages of Reference)	IID Limit for oral tablet [20]	Usual recommended concentration
Sodium starch glycolate	Disintegrant	[21] pp. 663-66	90 mg (Type A); 12 mg (Type B)	2-8 %
Synthetic red iron oxide	Colorant and UV-adsorbent	[21] pp. 340-42	NMT 0.1% in final formulation [22]	-
Titanium dioxide	White pigment and opacifier	[21] pp. 741-44	24.23 mg	-

Formulation Challenges

Rifapentine is known to convert into 3-formylrifamycin (3-RIF) by hydrolysis [23]. FDA review for Priftin® and its label recommends storage at room temperature and protection from high relative humidity [2]. The SDS from Sigma-Aldrich recommends the rifapentine API to be stored at 2-8°C [4]. The acidic nature of INH and other HCL/amine group containing excipient accelerates decomposition of rifapentine through the Maillard reaction. Thus, rifapentine drug substances should not be directly exposed to H and amine group donors such as INH or potential excipients containing amine/HCL group. Rifapentine interacts with INH to form isonicotynl hydrazone.

Efficacy, ADME, and Adverse Effects

Recent studies in murine infection models found that much shorter treatment times for tuberculosis could be achieved when oral rifapentine was dosed daily and substituted for rifampicin to treat active infection (3 months) and isoniazid (INH) to treat latent infection (2 months) [4, 8]. Thus, the substitution of current key antitubercular drugs (rifampicin and isoniazid) with ifapentine might radically alter tuberculosis treatment outcomes. The in vitro activity of rifapentine is 2-4 times that of rifampicin against a variety of clinical mycobacterial isolates. Rifapentine is bactericidal against actively growing bacilli, with a killing rate similar to that documented for rifampicin. The half life of rifapentine in humans is ~4-fold greater than rifampicin [24, 25]. The prolonged elimination half-life of rifapentine is likely due to its higher lipophilicity, which facilitates

tissue penetration of the drug and lack of biotransformation to inactive metabolites [26]. Absorption is enhanced when the drug is taken after a meal [18].

The apparent volume of distribution was found to be 70.2 ± 9.1 L in patients. Both, rifapentine and its active metabolite were found to bind with plasma proteins up to an extent of more than 90% in healthy volunteers. The major binding protein was human serum albumin.

Single dose whole body clearance indicated that 80% of the total dose was excreted from the body within 7 days. The drug is majorly excreted in feces and urine, as rifapentine and 25-desacetyl rifapentine. Conversion of rifapentine to 25-desacetyl rifapentine takes place by hydrolysis in the presence of microbiological esterase. Drug and the active metabolite cover 62% and 38% of the total activity against *Mycobacterium tuberculosis*.

Clinical studies were performed for active and latent tuberculosis infection. Patients with active tuberculosis infection were divided into two groups (n=361 in each group). The first group was labeled as Priftin® and the other as rifampin group. The first group received 600 mg Priftin® twice a week with three other first-line antitubercular drugs in the "intensive phase". The second group received a 600 mg daily dose of rifampin along with three first-line drugs. In the "continuation phase" the first group received a once a week dose of Priftin® in combination with INH, while the second group received a once a week dose of 900 mg of rifampin with INH at the same dose. Here, the first group showed overdosing which was two times greater than the second group. Similarly, adverse drug reactions were also observed at a higher rate for the first group. The relapse rate was higher for Priftin® group but patients were not resistant to rifampin. In the case of HIV-infected patients, relapse was observed along with rifampin resistance.

Similarly, the patients with LTBI were divided into two groups: the first group was labeled as Priftin® group and the second group as rifampin group. The Priftin® group received rifapentine and INH at a dose of 900 mg once-weekly while the rifampin group received only INH, 2700 mg per week. In this study, conversion of latent to active tuberculosis was found to decrease in the Priftin® group as compared to the rifampin group. The Priftin group showed the same results as in HIV-infected patients and in pediatric patients with LTBI. However, the Priftin® group patients (1/7) showed rifampin and INH resistance [2].

Bioavailability and Pharmacokinetics

US FDA has established a Biopharmaceutics Classification System (BCS) for immediate release (IR) of solid oral dosage forms for the purposes of requesting a waiver from having to perform a bioequivalence study in support of an abbreviated new drug application (ANDA). The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. According to the BCS, drug substances are classified as follows:

Class 1: High Solubility – High Permeability

Class 2: Low Solubility – High Permeability

Class 3: High Solubility – Low Permeability

Class 4: Low Solubility – Low Permeability

According to the US FDA BCS guidance [31], when the SDF is rapidly dissolving, demonstration of in vivo bioavailability (BA) or bioequivalence (BE) may not be necessary for drug products containing Class 1 and Class 3 drug substances. The ANDA manufacturer/applicant could request a biowaiver as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients.

Priftin® has a 70% reported bioavailability compared to the oral solution. Rifapentine is sparingly soluble in aqueous media and has a log P of 5.29 [27]. Although a specific BCS class for rifapentine is not reported in the literature, it could be classified as a BCS Class 2 compound based on its solubility and log P data.

The absolute bioavailability of rifapentine has not been determined.

The relative bioavailability (with an oral solution as a reference) of rifapentine after a single 600 mg dose to healthy adult volunteers was 70% [10]. The maximum concentration was achieved 5 to 6 hours after the administration of the 600 mg rifapentine dose. The administration of rifapentine with a high fat meal (850 total calories: 33 g protein, 55 g fat and 58 g carbohydrate) increased area under the curve (AUC) (0-∞) and Cmax by 43% and 44% respectively, compared to the dose administered under fasting conditions. When oral doses of rifapentine were administered once daily or once every 72 hours to healthy volunteers for 10 days, the single dose AUC (0-∞) value of rifapentine was similar to its steady-state AUCss (0-24h) or AUCss (0-72h) values, suggesting no significant auto-induction effect on steady-state pharmacokinetics of rifapentine. Steady-state conditions were achieved by day 10 following the daily administration of 600 mg rifapentine. The pharmacokinetic

parameters of rifapentine and 25-desacetyl rifapentine (active metabolite) on day 10 following oral administration of 600 mg rifapentine every 72 hours to healthy volunteers are contained in Table 3.

Table 3. Pharmacokinetics of rifapentine & active metabolite in healthy human volunteers (n=12)

Parameter	Rifapentine (Mean ± SD)	25-desacetyl Rifapentine (Mean ± SD)
C_{max} (µg/mL)	15.05 ± 4.62	6.26 ± 2.06
T_{max} (hr)	4.83 ± 1.80	11.25 ± 2.73
$AUC_{0\text{-}72\ hr}$ (µg*h/mL)	319.54 ± 91.52	215.88 ± 85.96
$T_{1/2}$(h)	13.19 ± 1.38	13.35 ± 2.67
$Cl_{p.o.}$ (L/h)	2.03 ± 0.60	-

One study included a randomized crossover design with 20 healthy male volunteers. Volunteers were administered rifapentine capsules of 600 mg. Mean pharmacokinetic parameters were calculated and comparison showed 92% relative bioavailability with bioequivalence between two formulations [28]. Another study investigated pharmacokinetic behavior of rifapentine in tuberculosis patients compared to healthy human volunteers. Rifapentine was administered as 450 mg capsules. Mean pharmacokinetic data concluded the equivalent behavior in both healthy as well as patients suffering from pulmonary tuberculosis [29]. A third study evaluated relative bioavailability and bioequivalence of rifapentine capsules at dose of 600 mg. All three studies reported randomized cross over design for studying bioequivalence of Rifapentine capsules [28-31]. It is suggested to perform bioequivalence of proposed generic product against the RLD (i.e. Priftin®).

Rifapentine has poor aqueous solubility, however its BCS class has not been reported. Rifampicin, a compound structurally similar to rifapentine, has been reported to belong to BCS class II [32]. The marketed formulation of rifapentine has a relative oral bioavailability of 70%. It is reported to have 1.4x food effect reflected by increased ~40% AUC when administered with a meal. 25-desacetyl-rifapentine is an active metabolite of rifapentine. It is ~90% plasma protein bound and has volume of distribution of 70.2 ± 9.1 L in patients. 80% of the total dose excretes in 7 days after single oral administration. Drug and the active metabolite contribute 62% and 38% of the total activity against *Mycobacterium tuberculosis*.

Process Equipment Selection

Rifapentine is red-orange colored dye. Therefore rifapentine containing blend handling may require dedicated equipment and processing rooms. Rifapentine can be formulated using a wet granulation process followed by compression. Major unit operations in wet granulation include milling, sieving, blending, granulation, drying, compaction, and coating. Milling is an optional unit operation and may be required if the particle size of the raw material is higher than the required specification. Airjet mill or Quadro mill can be used for milling. V blender, double cone blender, bin blender, or octagonal blender can be used for blending. Rapid mixing granulator (RMG) and fluidized bed dryer can be used for granulation and drying, respectively. Dried granules can be compacted using a rotary press to obtain the tablets.

Manufacturing Process

Based on the knowledge regarding the API and the excipients utilized by Priftin®, the following manufacturing process guideline is provided to the ANDA manufacturer.

Wet granulation process is most commonly used to obtain readily compressible granules. The first step may be the milling of raw material. However, this is an optional step based on the particle size of the supplied raw material. Milled powder is then subjected to sieving to achieve uniform particle size. Bulk powder obtained after sieving is blended with appropriate inactive ingredients. Granulating fluid containing the binder is added to the dry powder blend in RMG to obtain a wet dough mass and subsequently the granules. The granules are then dried using the equipment like a fluidized bed dryer. The dried granules are mixed with extra-granular inactive ingredients in a blender and then compressed in a tablet press to obtain the final formulation.

Scale-up Challenges

The scale up of rifapentine requires higher capacity conventional equipment for wet granulation that includes blender (double cone/v/octagonal/bin), granulator (RMG), dryer (fluidized bed dryer), tablet press, etc. Best practices for the development, scale-up, and post-approval change control of IR dosage form are documented in a recently published white paper.[33] Criteria for submission of required data for proposed scale up and post approval changes (SUPAC) has been well documented in FDA guidance published in 1995 [28]. SUPAC documentation for equipment used in individual unit operation has also been addressed by recent FDA guidance.[29] SUPAC-IR

requirement for up to 10X scale up is specified in section V.B of "Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, *In-Vitro* Dissolution Testing, and *In-Vivo* Bioequivalence Documentation". The scale up (up to 10X) may be deemed a Level 1 change if it meets the prescribed criteria in FDA 'question-answer document' for SUPAC-IR [30]. Level 1 changes include a change in batch size, up to and including a factor of 10x the size of the pilot/bio-batch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with CGMPs; and 3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es). Level 1 changes require submission of an annual report to the drug application (NDA/ANDA) with a long-term stability study of at least one production batch, while no *in vivo* bioequivalence study is required.

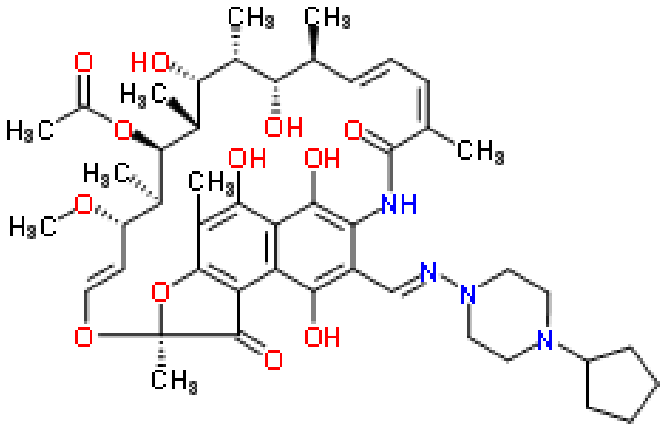
Analytical Profile

Rifapentine is a semi-synthetic rifamycin antibiotic similar in structure to rifampin. Rifapentine is approved by the US FDA as a first-line drug for once or twice-weekly dosing in the treatment of TB [23, 34].

The Active Pharmaceutical Ingredient (API)

The API is available in crystalline solid form in brick-red to reddish brown, crystalline powder. It is practically odourless. Its oral bioavailability is increased by ingestion of food. The published crystalline forms of rifapentine are limited to its methanol solvate, which are unsuitable for pharmaceutical use [36, 37].

Chemical Structure/Formula



Molecular Formula $C_{47}H_{64}N_4O_{12}$

Stereochemistry [23]

Stereochemistry	Absolute
Optical activity	Unspecified
Additional stereochemistry	No
Defined stereocenters	9 / 9
EZ centers	1
Charge	0

Name [8]

IUPAC Name

(7S,9E,11S,12R,13S,14R,15R,16R,17S,18S,19E,21Z)-26-[(1E)-[(4-Cyclopentylpiperazin-1-yl)imino]methyl]-2,15,17,27,29-pentahydroxy-11-methoxy-3,7,12,14,16,18,22-heptamethyl-6,23dioxo-8,30-dioxa-24-azatetracyclo[23.3.1.1[5].0[6]] triacont a-1,3,5(28),9,19,21,25(29),26-octaen-13-yl-acetate

Others [8]

CAS: CAS-61379-65-5.
Molecular Weight: 877.04
Chemical Name: Rifamycin, 3-[[(4-cyclopentyl-1-piperazinyl)imino]methyl]-; (2) 3-[N-(4-Cyclopentyl-1-piperazinyl)formimidoyl] rifamycin.

Physical Properties

Log P:

4 [4]

Water Solubility

2.13e-02 g/L [4]

Refractive Index for Rifapentine

1.6 [4]

Solubility

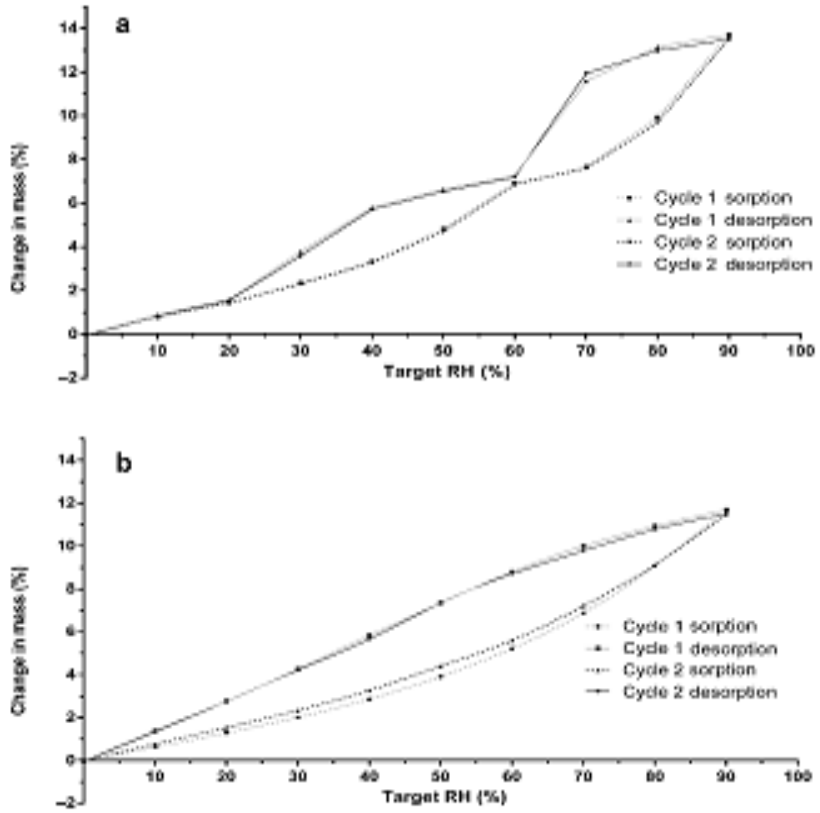
The solubility of rifapentine in methanol, ethanol, acetone, chloroform, and dichloromethane was measured at temperatures ranging from (278° to 323° K) under atmospheric pressure. The solubility of rifapentine in the above solvents increased in the following order: chloroform, methanol, dichloromethane, ethanol, acetone. The experimental solubility data were well-correlated with the data, calculated by means of a semi empirical equation [37]. As documented above, rifapentine solubility is poor.

Moisture Sorption

The moisture sorption profiles of the amorphous and crystalline sample powders were analyzed using a dynamic vapor sorption (DVS) instrument operated at 25°C under continuous nitrogen flow. Ten milligrams of each powder was exposed to dual moisture ramping cycle of 0%–90% relative humidity (RH) with 10% RH increments. Mass changes were recorded over time. Equilibrium moisture content was defined as a d*m*/d*t* of 0.002% per minute [38].

Moisture sorption profiles for both powders were readily reproduced during the second moisture exposure cycle, suggesting physical stability against moisture uptake. Although the amorphous form showed a typical moisture sorption profile, the double sigmoid profile for crystalline rifapentine was unexpected. It could be interpreted as a multihydrate sample, whereby the sample first forms a monohydrate followed by a dihydrate. Alternatively, it could mean that different particles, in particular the small particles or parts of the particle (such as the surface) hydrated first, followed by hydration of the particles' core. Moisture sorption isotherms for (a) crystalline and (b) amorphous rifapentine with dual cycle humidity ramping from 0% to 90% RH are shown in Figure 1.

Figure 1. Moisture sorption isotherms for (a) crystalline and (b) amorphous rifapentine

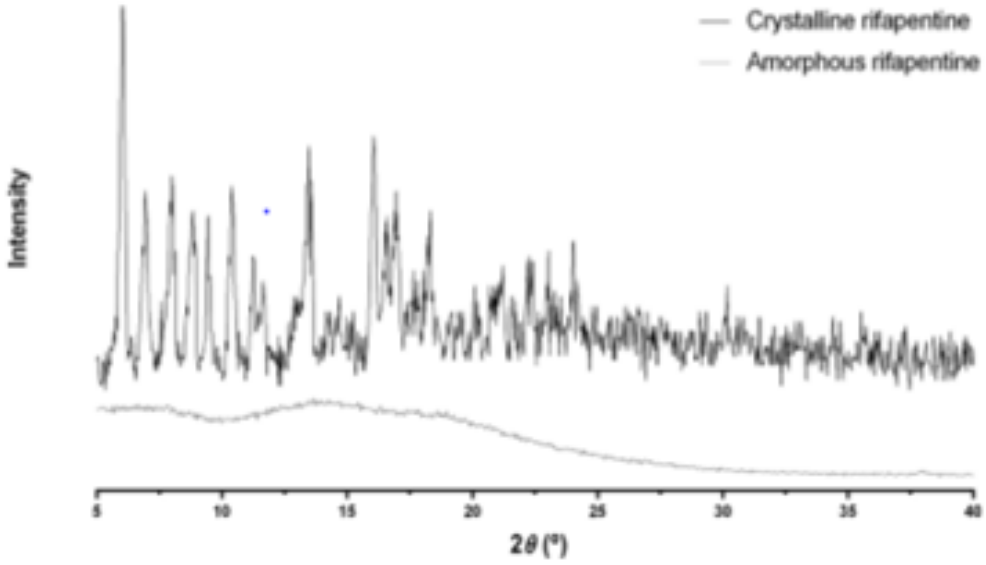


Characterization by Various Techniques

X – Ray Diffraction Study

X-Ray Diffraction technique was used to analyse crystallinity of the dry powders and showed multiple strong intensity peaks and a typical "halo" pattern for the crystalline and amorphous Rifapentine powder, respectively [38], as shown in Figure 2.

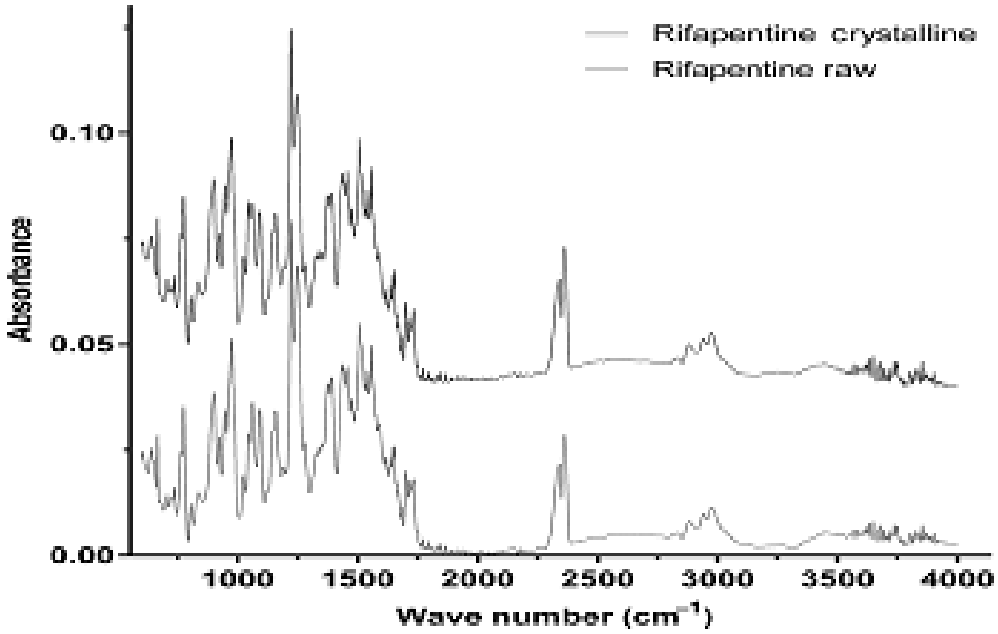
Figure 2. X-ray diffractogram for crystalline and amorphous rifapentine



FTIR Spectrum of Rifapentine

The comparative study highlighted that the crystalline form of rifapentine was free of organic solvent and suitable for clinical use [38]. The FTIR spectrum of rifapentine is shown in Figure 3.

Figure 3. IR spectrum of rifapentine in crystalline and raw forms



Mass Spectrum

Sixteen (16) different ionization and sample introduction methods have been compared for rifapentine in the Mass Spectrometer System. Direct sample introduction with electron impact, chemical ionization, or field ionization lead to nearly complete (thermal) degradation of the sample. All other sample-introduction methods (except PB with EI) lead to easily identifiable molecular ion species, with no or only slight thermal decomposition. This suggested that thermal decomposition of rifapentine occurred when a solid sample was evaporated by relatively slow heating and the vapour could come into contact with the hot metal walls of the ion source. This could also explain the lack of success with PB in EI. The beam of sample vapour probably hit the wall of the source, which lead to degradation [39].

The mass spectra of rifapentine obtained with the thermo spray interface with both positive and negative ionization modes are shown in Figure 4.

Electrospray ionization-ion trap mass spectrometry of rifapentine provided the protonated molecular ion at m/z 877.32 and an ion at m/z 845.28 in the MS^2 mode, which corresponded to the even electron mass loss of CH_3OH (32 Da) from position 27. Fragmentation of the ion at m/z 845.28 in the MS^3 mode produced major ions with m/z values at 785.20 and 453.12. The former signal corresponded to an even electron mass loss of CH_3COOH (60 Da) from position 25. The ion at m/z 453.12 corresponds to the breakup of the macrocycle figure given below. Fragmentation of the ion at m/z 453.12 in the MS^4 mode gives a major ion with m/z value at 299.09. This latter signal corresponded to an even electron mass loss of the N-[4-cyclopentyl-1-piperazinyl] entity (154 Da).

The three even electron mass losses that are seen in metabolic transformations of these macrocyclic antibiotics are illustrated in Figure 5. These observations illustrate that, in certain cases, electrospray ionization-ion trap mass spectrometry of the cleavage of functional groups as even electron mass losses may predict the locations of particular metabolic transformations, even though losses of the functional groups may not correspond exactly with the observed metabolites, e.g., the even electron mass loss of CH_3COOH (60 Da) for rifapentine parallels formation of the 25-desacetyl metabolite, which corresponds to the conversion of the CH_3COO substituent to that of OH, an overall mass loss of 42 Da [40].

Figure 4. Positive (a) and negative (b) ion mass spectrum of rifapentine obtained with thermospray interface

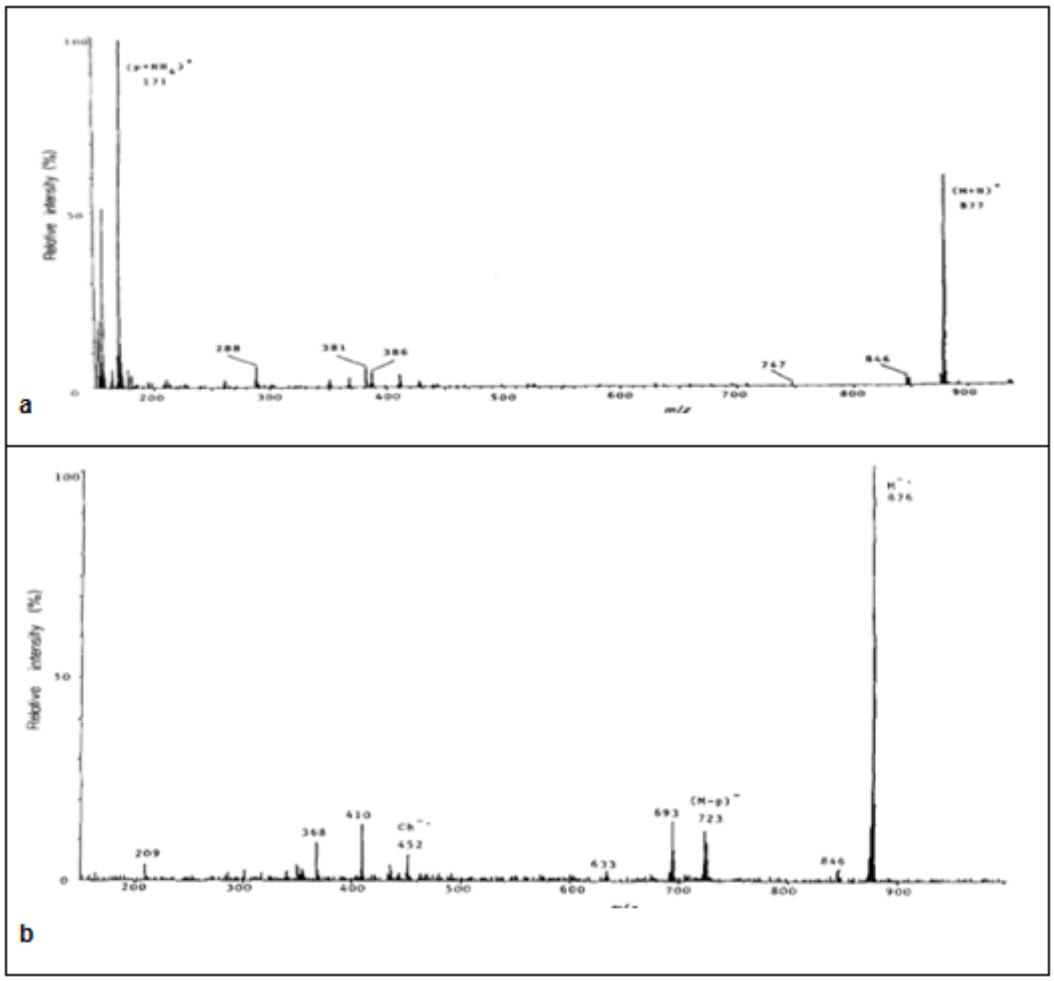
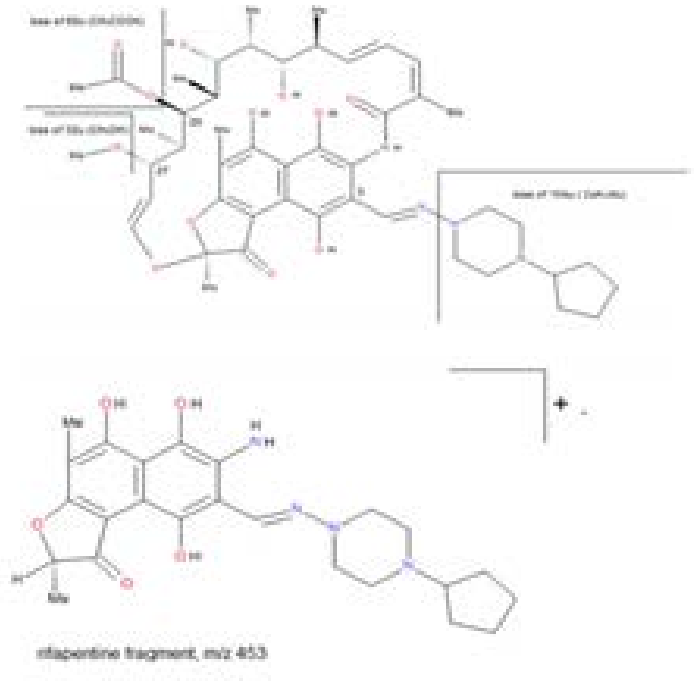


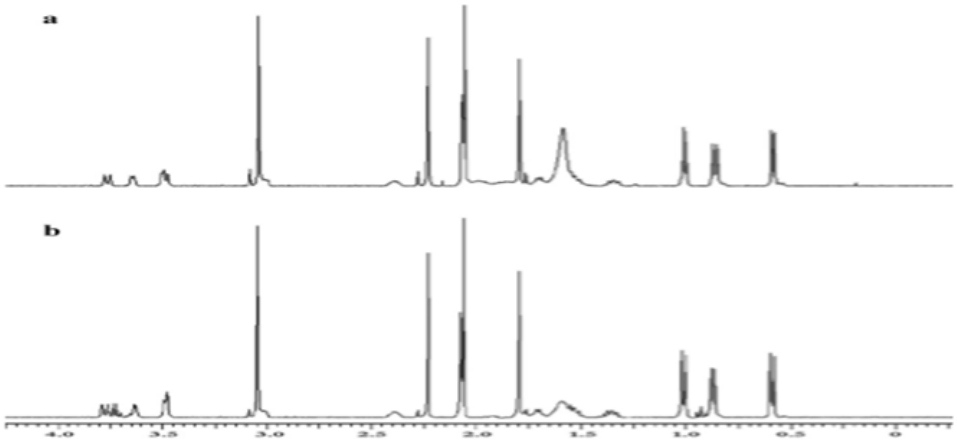
Figure 5.Fragmentation of rifapentine



Nuclear Magnetic Resonance Spectrum

Proton nuclear magnetic resonance (1H NMR) analyses were recorded at 400 MHz on Spectrometer System with a SMS autosampler. NMR spectra were run at SW of −2 to 14 ppm, 256 transients, and were referenced to residual chloroform in deuterochloroform ($CDCl_3$) at 7.27 ppm. Approximately 10 mg of unprocessed raw rifapentine and crystalline were solubilised in $CDCl_3$ for analysis. Chemical shifts are quoted in ppm.

Figure 6. NMR spectra for (a) crystalline and (b) raw unprocessed Rifapentine in $CDCl_3$

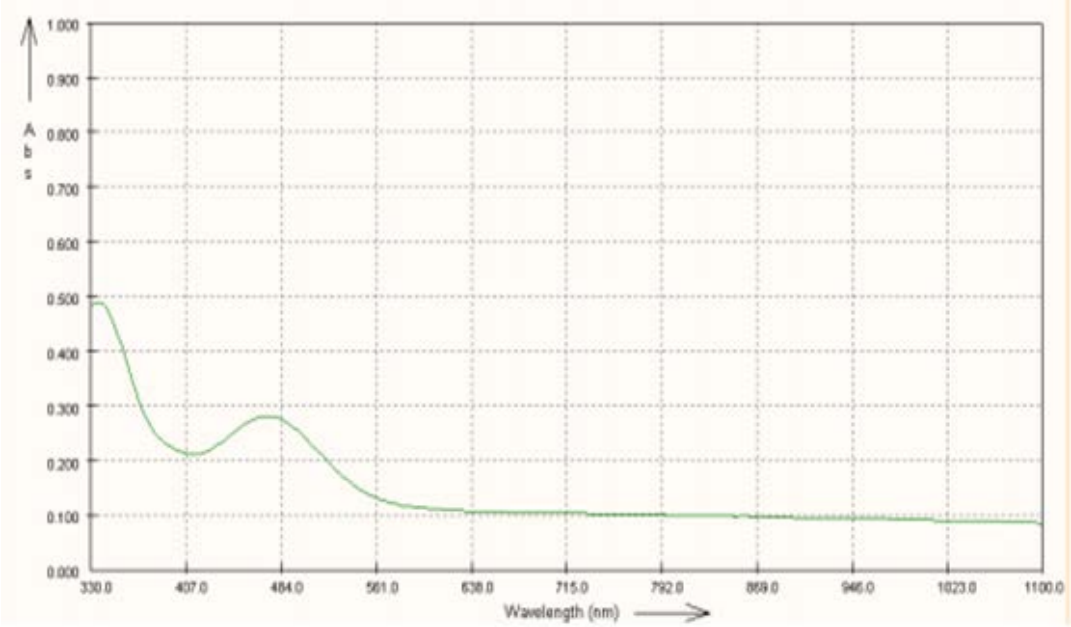


Both powders showed a broad endotherm between 25°C and 140°C as shown in Figure 6 likely because of the loss of residual water from spray drying, which corresponded with the NMR data. A baseline shift at around 161˚C–173°C for the amorphous form represented melting followed by decomposition. In contrast, a much more defined endothermic peak at 171°C associated with decomposition was seen for the crystalline powder [38].

Ultra Violet & Visible spectrum

Rifapentine is an ultra violet-visible spectrum absorbing molecule with specific chromophores in the structure that absorb at a particular wavelength. The ultra violet-visible spectrophotometric method was employed for the quantitative determinations of rifapentine. The absorption spectrum of rifapentine in 0.1N HCL is shown in Figure 7 [14].

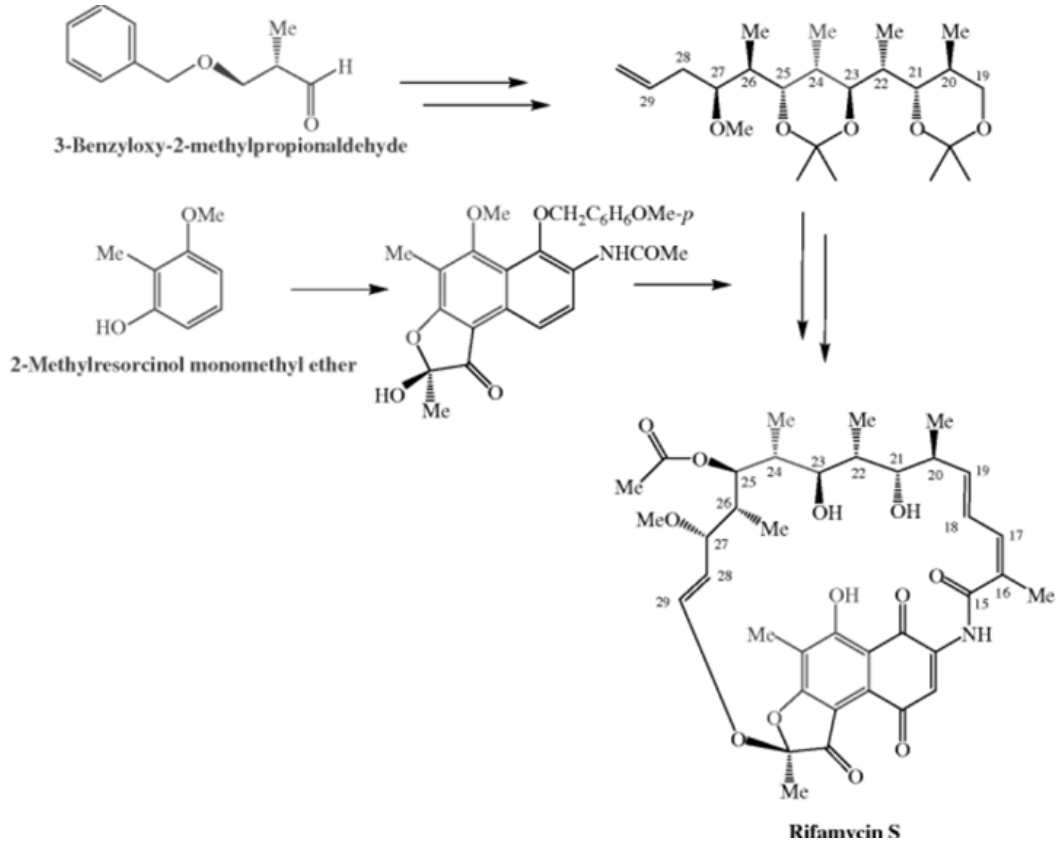
Figure 7. Absorption spectrum of Rifapentine showing maximum absorbance at 478 nm



Synthesis of Rifapentine

The first total synthesis was reported by Kishi and co-workers as early as 1980, in 62 steps with the ansa chain being derived from 3-benzyloxy-2-methylpropionaldehyde and the aromatic fragment from 2-methylresorcinol monomethyl ether. But, as shown in scheme 1 [41] the overall yield was less than 0.01%.

Scheme 1. Kishi's total synthesis of rifamycin S

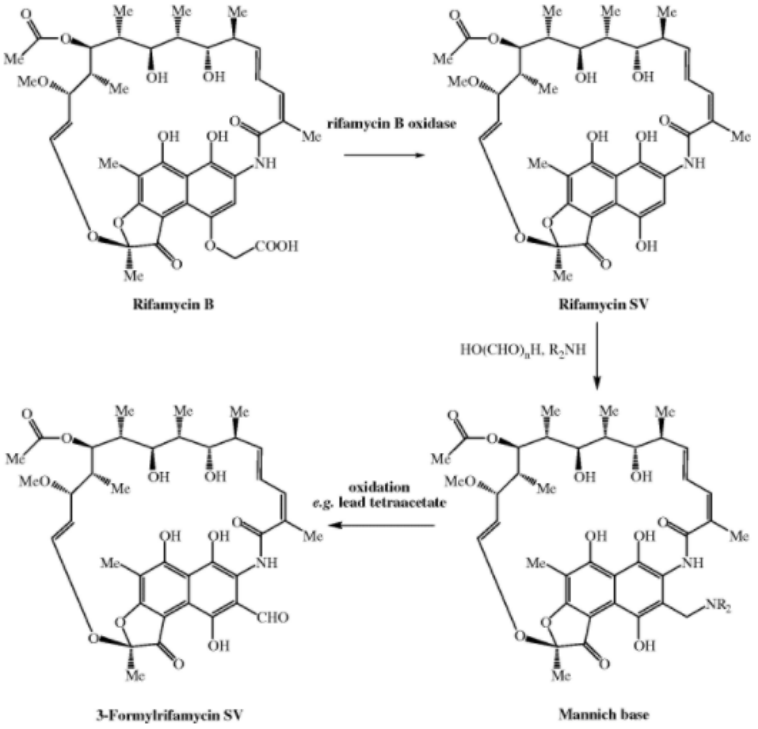


The production of rifamycins by such total syntheses is obviously impractical as the obtained quantities are too small, and such a sequence could be too costly.

Thus, rifampicin and rifapentine are known as semi-synthetic antibacterial agents that are prepared by a combination of fermentation and synthesis. Fermentation of a microbial broth produces the complex core structure that contains the ansa ring attached to the naphthofuran ring system, which is then elaborated to give the derivatives used clinically in a series of relatively simple chemical transformations. The key intermediate in the preparation of rifampicin and rifapentine is 3-formylrifamycin SV, which was originally obtained from the decomposition of some of the early, chemically unstable analogues that were synthesised for biological evaluation.

The enzyme based oxidation method uses rifamycin B oxidase, where fermentation of *A. mediterranei* gives rifamycin B. rifamycin B is converted to rifamycin SV. Rifamycin SV leads to the formation of 3-formylrifamycin SV *via* mild oxidation of Mannich base formed by the reaction with paraformaldehyde and a secondary amine as shown in scheme 2 [42].

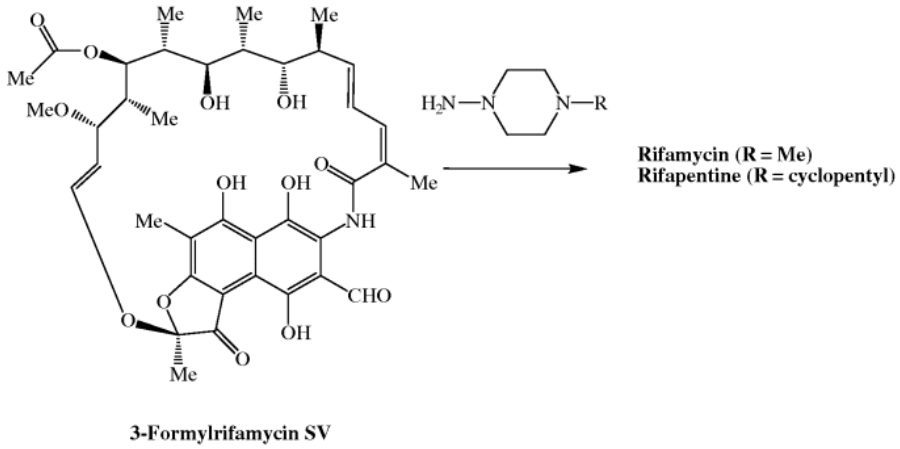
Scheme 2. Synthesis of key semisynthetic intermediate 3-formylrifamcin SV



[Organic solvents and catalysts used: Rifamycin B oxidase (fungal enzyme), Paraformaldehyde, oxidation by lead tetra acetate]

The synthesis of rifapentine then involves the simple condensation of a hydrazine with this aldehyde as shown in scheme 3 [42].

Scheme 3. Synthesis of Rifapentine



[Reagent used: 4-Cyclopentyl-1-piperazinamine,THF at room temperature]

Latest developments give two more efficient and "greener" process routes for the synthesis of rifamycin S for which the reaction can be carried out under mild conditions and avoids the waste of halogenated solvents.[43]

By employing process 1, study showed that 70% of rifamycin S product can be obtained in an aqueous solution containing 37.5% MeOH with APS after 4 h. Process 1 was developed to fit the needs of the technical process currently used for the rifamycin S production and could be directly applied to existing rifamycin plants.

In process 2, 132 mM of rifamycin B product can be obtained after extraction from the fermentation broth containing pure MeOH. The utilization of this high concentration is indicative of a potential large-scale process. With the addition of small amounts of buffer and ammonium persulfate (APS), 68% of rifamycin S was formed in 20 min.

Reaction conditions: 40 mg of rifamycin B (0.052 mmol) and 12 mg (0.052 mmol) of APS in MeOH, the reaction was performed at 60 °C for 15 min.

Analysis by Reverse Phase (RP) HPLC Methods

A number of reverse phase (RP) High Performance Liquid Chromatography (HPLC) methods have been reported in literature for rifapentine. A well-developed RP HPLC method reported for the estimation of rifapentine in bulk and pharmaceutical dosage form is described here. For HPLC method, Column: C_{18} (4.6 ID x 250 mm) in isocratic mode with mobile phase containing acetonitrile 0.01M KH_2PO_4 buffer pH (6.0) in ratio of (80:20) v/v was used. The flow rate was 0.8 ml/min with injection volume of 20 µl and the effluent was monitored at 478 nm. Retention time for rifapentine was found to be 5.00 ± 0.1 minute.

The method was validated for parameters like accuracy, linearity, precision etc, as per ICH guidelines. The values of relative standard deviation and % recovery were found to be satisfactory, indicating that the proposed method is precise and accurate. Therefore, this method can be used by the ANDA manufacturer for the routine analysis of rifapentine in bulk and pharmaceutical formulation upon carrying out the necessary analytical method validation in their own laboratory, as per ICH guidelines [44].

The reported regression analysis data and summary of validation parameter for the RP-HPLC method parameters results are provided in Table 4.

Table 4. RP-HPLC Method Parameters

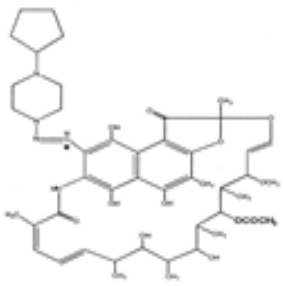
Linearity range (µg/ml)	20-70 µg/ml
Slope (m)	3098
Correlation coefficient	0.9992
Intercept (c)	1960
Limit of quantitation (µg/ml)	0.684 µg/ml
Limit of detection (µg/ml)	0.225 µg/ml
Precision (%RSD)	
Intra-day precision	0.14
Inter-day precision	0.13
Ruggedness	Rugged

Other Reported Methods

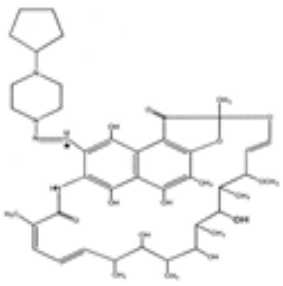
HPLC methods have been developed for the determination of rifapentine as a result of advantages such as a short turnaround time, method reliability, sensitivity, and specificity [45, 46]. All these methods are time consuming and tedious because of the deproteinization or liquid-liquid extraction steps required for sample clean-up. These problems can be avoided by using a column-switching technique [47-51], which allows on-line sample clean-up with no extraction step.

Rifapentine and Its Impurities with Their Availability

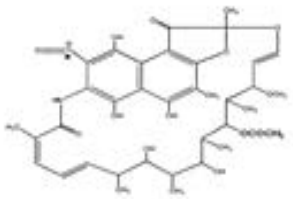
Rifapentine and its related impurities have the following structures:



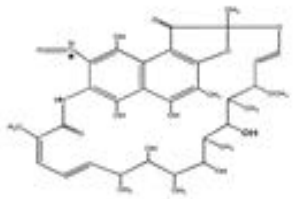
Rifapentine



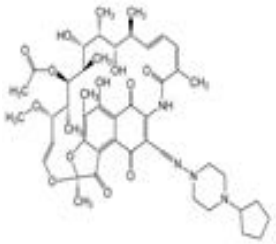
25-desacetyl-rifapentine



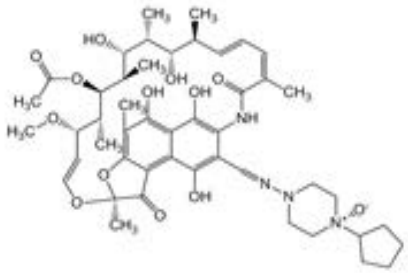
3-formyl-rifapentine



3-formyl-25-desacetyl-rifapentine



Rifapentine quinone



Rifapentine n-oxide

Rifapentine and its related impurities are commercially available from most of the impurity suppliers across the globe and can be accessed online. A few of them are TLC Pharmaceutical Pvt.Ltd., Pharmaffiliates Analytics & Synthetics (P) Ltd, Sigma Aldrich, TRC Chemical, etc.

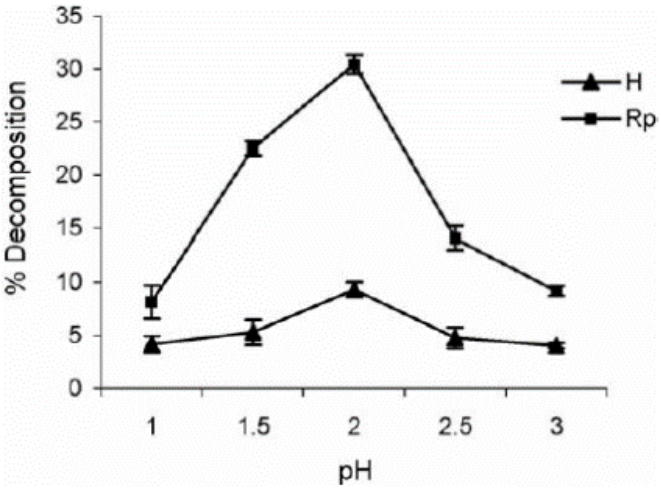
Stability of Rifapentine

Behavior of rifapentine with isoniazid

Kinetic decomposition studies have been carried out at various pHs. There has been evidence of potential interactions of rifamycins with isoniazid (INH), especially at acidic pH. A stock solution of 1M HCl was prepared by dilution of concentrated HCl. The same was standardized against 1M NaOH, which was standardized previously against 1M oxalic acid. The stock was diluted with water to achieve concentrations of 0.1, 0.03, 0.01, 0.003 and 0.001M HCl (pH 1, 1.5, 2, 2.5 and 3, respectively). For decomposition at various pHs, rifapentine (22.5 mg) and INH (15 mg) were first weighed accurately and dissolved in 2ml of methanol. The mixture was then diluted with a solution of specific pH up to 25 ml. An aliquot (2 ml) of this solution was withdrawn, diluted to 10 ml with methanol and analyzed by HPLC. The remaining solution was maintained in a water bath at 37 ˚C for 50 min and then subjected to HPLC by the same method. The percentage degradation of rifapentine and H were calculated from the difference in peak areas of initial and 50 min samples. The studies were conducted in triplicate [23]. The kinetics of degradation at different pH conditions for rifapentine is similar to that observed for rifampicin. Both drugs, rifapentine and INH, exhibit a bell shaped

degradation profile with maximum degradation occurring at pH 2, the loss of rifapentine and H being ~30 and ~9%, respectively as shown in Figure 8 [52].

Figure 8. Profile of pH-dependent decomposition of rifapentine and INH



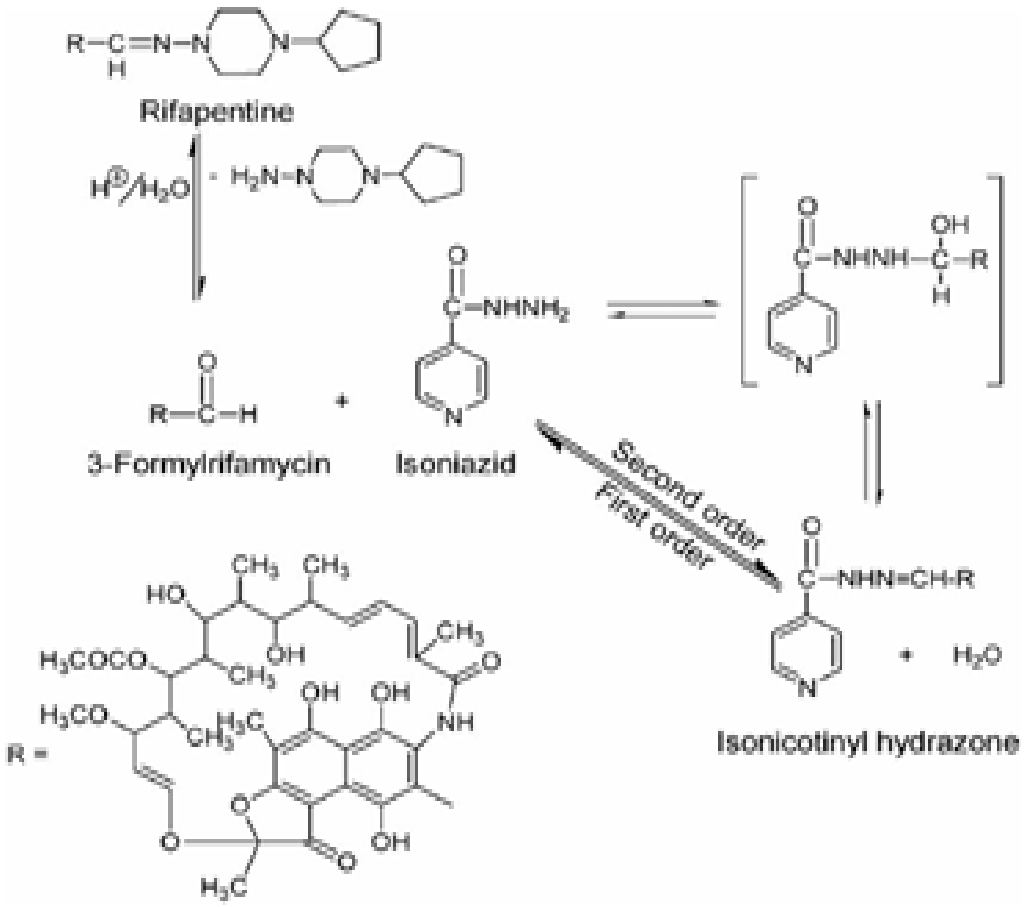
Under alkaline conditions (pH of 7.5 to 9.0), Rifapentine will oxidize if oxygen is present, becoming rifapentine-quinone. Rifapentine is most stable at near neutral pH. The addition of ascorbic acid to the solution increases the solubility of rifapentine and decreases its oxidation [50]. These reactions are similar to that observed for rifampicin.

Mechanism of Degradation and Degradation Products

Under acidic pH, rifapentine converts to 3-formyl rifamycin and 4-cyclopentylpiperazin-1-amine. The former (3-formyl RIF) interacts with INH to form isonicotinyl hydrazone by a similar mechanism to that observed in rifampicin. The reaction results in the formation of hydrazone and is reversible. Therefore, there is minimal decomposition of isoniazid. However it reacts with 3-formyl RIF, and undergoes degradation at the expense of latter. Hence, there is a loss in effectiveness of both drugs at acidic pH [24, 53].

Figure 9 highlights the potential degradation pathway of rifapentine T at acidic pH. Under alkaline conditions rifapentine-quinone is formed in the presence of oxygen [54].

Figure 9. Scheme for interaction of Rifapentine with H under acidic condition



B. Prasad et al. 2010 also did a study on the identification and characterisation of metabolites of rifapentine and did a similar metabolite profile in all *in-vitro* and *in vivo* matrices. A total of twenty six metabolites were detected and separated. Other than four known metabolites already reported in literature, twenty two new metabolites were identified and characterised [23].

Stability in Powder Form and Formulation Products

Dry Powder Stability

To evaluate the physico-chemical stability testing, the dry powders were stored in glass scintillation vials protected from light, and kept at either 0% or 60% RH at 25◦C. Powders tested at 0% RH, were stored under vacuum in a desiccator with silica gel desiccant beads. Powders tested at 60% RH were stored in a climate controlled

cabinet. At 1 and 3-month time points, the aerosol dispersion properties and drug content of the dry powders were assessed using the aforementioned methods.

No differences were observed in particle morphology, in vitro aerosol deposition profile, and fine particle fraction (FPF) of the amorphous powder after 1-month storage. However, powder colour change and an oxidation product of rifapentine were identified signifying that the amorphous powder was chemically unstable at ambient (60% RH) and dry (0% RH) storage conditions. In contrast, chemical degradation of the crystalline rifapentine powder was not detected after storage for up to three months, at either humidity level. However, the FPF of the crystalline powder increased with storage time as powder deposition shifted from device to stage 5. This could be due to changes over storage time including dissipation of electrostatic charge or a reduction in surface energy by relaxation of the crystal structure. Interestingly, within each time-point, there was no statistical difference in the deposition profile of the powder stored at different conditions (0% and 60% RH) [38].

Table 5. Mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and fine particle fraction (FPF) for crystalline and amorphous rifapentine dry powders stored up to 3 months at 25 ° C (n=3; mean ± SD)

		1 Month		3 Months	
Relative Humidity (%)	Time 0	0	60	0	60
Crystalline MMAD (μm)	1.68 ± 0.03	1.66 ± 0.03	1.68 ± 0.04	1.66 ± 0.09	1.65 ± 0.02
GSD	1.72 ± 0.00	1.71 ± 0.01	1.70 ± 0.02	1.75 ± 0.04	1.73 ± 0.01
FPF%	83.2 ± 1.2	84.8 ± 1.9	86.7 ± 1.1	88.0 ± 2.3	90.0 ± 0.1
Amorphous MMAD(μm)	1.92 ± 0.10	1.93 ± 0.09	1.96 ± 0.01	------	------
GSD	1.99 ± 0.02	1.96 ± 0.05	1.86 ± 0.02	------	-------
FPF%	68.8 ± 2.1	72.4 ± 5.2	70.2 ± 1.1	-------	--------

Polymorphism of Rifapentine

The hydrohalides of rifapentine showed polymorphism depending on the solvent system used for its crystallization and exists in crystalline polymorph form or an amorphous form. Two crystalline forms had been identified. Both show high stability during storage or with handling for the manufacture of the solid dosage unit forms. The crystalline modification of rifapentine mono hydrochloride showing melting point at 192°C has been identified as Form I while the crystalline modification showing a broad endotherm in the temperature range 180-220°C has been identified as Form II. Transformation of Form I into the amorphous form requires a prolonged grinding in a mortar while the conversion of Form II into the amorphous form occurs in a shorter amount of time [55].

Assay from Biological Samples

A RP HPLC method with column switching has been developed for the determination of rifapentine in serum. The serum samples were injected onto a pre-column packed with Corasil RP C_{18} (37-50 pm) after simple dilution with an internal standard in a 1% ascorbic acid solution. Polar serum components were washed out using 0.05 M phosphate buffer. After valve switching, the concentrated drugs were eluted in the back-flush mode and separated by a Bondapak C_{18} column with a acetonitrile-tetrahydrofuran-0.05 M phosphate buffer (PH 7.0) (42:5:53, v/v/v) as the mobile phase. The method showed excellent precision with good sensitivity and speed, and had a detection limit of 0.1 pg/ml. The total analysis time was less than 25 min and the mean coefficients of variation for intra- and inter-assay were less than 4.8%. The method has been successfully applied to serum samples from dogs after the oral administration of rifapentine [47].

The applicability of the direct injection HPLC method to measure rifapentine and its metabolite in plasma was demonstrated. The method has an adequate precision and accuracy at plasma levels from 0.94 to 60.54 pg/ml for rifapentine and from 0.47 to 30.08 pg/ml for its metabolites. The good correlation for about 450 samples between the results obtained with the HPLC method and a microbiological assay shows that either method can be used when assessing the total level of antibiotic in human plasma. However, under conditions that may interfere with a microbiological assay (such as the presence of other antibiotics) or when differentiation between the parent compound and the metabolite is necessary, the HPLC method is preferable [47].

Availability of Pharmacopoeia Standards

No pharmacopeial monograph has been reported for the rifapentine so far.

Handling and Storage Conditions

Precautions for safe handling: Avoid contact with skin and eyes. Avoid formation of dust and aerosols. Provide appropriate exhaust ventilation at places where dust is formed.

Conclusion

Rifapentine, a drug used in the treatment of tuberculosis in combination with one or more other anti-tuberculosis drugs, presents several product development, manufacturing, and regulatory hurdles. Rifapentine is a red-colored dye and, as such, proper cleaning procedures are critical to control and demonstrate prevention of cross-contamination. In practice, this requires that the product be manufactured using dedicated equipment and rooms which can be financially, technically, and operationally challenging for manufacturers interested in such low-margin products. Additionally, chemical interaction between rifapentine and other acidic anti-TB drugs, such as INH, require careful selection of neutral excipients to improve the stability of the drug combination formulation. Spray-coating, granulation of the API, or use of a bilayer technology are possible solutions but can also be very challenging for generic manufacturers to produce due to the cost and technical know-how required.

In addition, there are no specific monographs for rifapentine API or FPP. It has proven difficult for generic manufacturers to develop validated method to characterize the drug substance and impurities.

Finally, there is no specific regulatory guidance from EMA, US FDA, or the WHO Prequalification Team for rifapentine bioequivalence study. BCS designation for rifapentine has not been reported. As of the date of publication, there are no quality-assured suppliers of rifapentine API for the public health market and no approved generic sources.

This product information report summarizes the available literature and provides expert scientific analysis of the physicochemical, biopharmaceutics, pharmacokinetics and toxicological properties, API synthesis, analytical, formulation, and manufacturing of rifapentine. It is expected that the PIR will provide critical information and guidance to manufacturers, as well as stakeholders concerned with access and supply of priority essential medicines.

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