A REVIEW ON :FACTORS INFLUENCING THE VARIABLE BIOAVAILABILTY OF RIFAMPICIN: A BIOPHARMACEUTIC AND PHARMACOKINETIC

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ABSTRACT:

Rifampicin is a key first-line antitubercular drug widely used in the treatment of tuberculosis. Despite its high therapeutic importance, considerable variability in its bioavailability has been observed among patients, which may affect treatment outcomes and contribute to drug resistance. The biopharmaceutic and pharmacokinetic properties of rifampicin play a significant role in determining its absorption, distribution, metabolism, and elimination. Factors such as poor aqueous solubility, formulation characteristics, food interactions, gastrointestinal conditions, and patient-specific physiological differences can influence the extent and rate of drug absorption. Additionally, rifampicin undergoes hepatic metabolism and exhibits autoinduction of drug-metabolizing enzymes, leading to changes in its pharmacokinetic profile during prolonged therapy. Variability in bioavailability may result in subtherapeutic plasma concentrations, reducing therapeutic efficacy. Understanding the relationship between biopharmaceutic factors and pharmacokinetic behavior is essential for optimizing dosage regimens and improving clinical outcomes. This review highlights the major causes of variable bioavailability of rifampicin and discusses strategies to enhance its therapeutic performance through improved formulation approaches and individualized treatment considerations.

KEYWORDS: Rifampicin, Bioavailability, Biopharmaceutics, Pharmacokinetics, Tuberculosis, Drug Absorption, Autoinduction.

1. INTRODUCTION:

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide despite the availability of effective chemotherapy and global control programs [1,2]. The emergence and spread of drug-resistant tuberculosis (DR-TB), particularly rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB), have become major challenges to tuberculosis control efforts globally [1,3]. Rifampicin resistance is defined as resistance to rifampicin detected by phenotypic or genotypic methods, with or without resistance to other first-line anti-tuberculosis drugs. MDR-TB is characterized by resistance to at least both rifampicin and isoniazid, the two most potent first-line anti-TB agents [1,3]. The increasing prevalence of MDR-TB is often associated with inadequate treatment, poor patient adherence, inappropriate prescribing practices, and the use of substandard drug formulations [1,4].

Rifampicin is a cornerstone of modern tuberculosis chemotherapy owing to its potent bactericidal activity against *Mycobacterium tuberculosis* and its ability to shorten treatment duration [4,5]. It is commonly administered as part of fixed-dose combination (FDC) formulations containing isoniazid, pyrazinamide, and ethambutol [2,6]. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease

(IUATLD) recommend the use of FDCs because they improve treatment adherence, reduce pill burden, minimize prescription errors, and simplify drug procurement and supply management [2,6]. However, concerns regarding the variable bioavailability of rifampicin in some FDC formulations have raised questions about their therapeutic effectiveness and their potential contribution to treatment failure and drug resistance [6,7].

The success of anti-tuberculosis therapy depends not only on the antimicrobial potency of the drugs but also on their pharmacokinetic properties, particularly bioavailability [5,8]. Bioavailability determines the extent and rate at which a drug reaches systemic circulation and becomes available at the site of action. Reduced rifampicin bioavailability may result in inadequate plasma concentrations, leading to poor therapeutic response, delayed sputum conversion, relapse, and the emergence of resistant strains of *M. tuberculosis* [8,9].

Considerable interindividual variability in rifampicin exposure has been reported among patients receiving standard doses of the drug [8,10]. Factors contributing to this variability include differences in formulation characteristics, age, sex, body weight, genetic polymorphisms, disease status, and concomitant medications [8,10,11]. Such variability has led to increasing interest in optimizing rifampicin dosing strategies to achieve consistent therapeutic drug concentrations and improve clinical outcomes [12,13].

According to the Biopharmaceutics Classification System (BCS), rifampicin is classified as a Class II drug, exhibiting low aqueous solubility and high permeability [4,6]. Its absorption is highly dependent on dissolution characteristics, making formulation quality an important determinant of systemic drug exposure [6,7]. Following oral administration, rifampicin is rapidly absorbed and extensively metabolized in the liver to form 25-desacetylrifampicin, an active metabolite that retains significant antimycobacterial activity [4,10]. Rifampicin also exhibits nonlinear pharmacokinetics and autoinduction of drug-metabolizing enzymes, resulting in changes in drug exposure during prolonged therapy [17,18].

HIV co-infection further complicates the pharmacokinetics of rifampicin and tuberculosis treatment outcomes [11,20]. HIV-associated gastrointestinal abnormalities, chronic inflammation, and altered physiological conditions may affect rifampicin absorption and systemic exposure. Several studies have reported reduced rifampicin concentrations in HIV/TB co-infected patients, although findings remain inconsistent across populations [11,19]. Additionally, genetic variations in drug transporters such as P-glycoprotein and OATP1B1 may contribute to pharmacokinetic variability and influence rifampicin disposition [10,20].

Given the critical role of rifampicin in tuberculosis treatment and the growing evidence of pharmacokinetic variability, understanding the factors affecting its bioavailability is essential for optimizing therapy. This review aims to examine the biopharmaceutic and pharmacokinetic determinants of rifampicin bioavailability, evaluate the impact of formulation-related and patient-related factors, and discuss strategies for improving rifampicin exposure to enhance therapeutic outcomes and reduce the burden of drug-resistant tuberculosis.

1.1 BIOAVAILABILTY

Bioavailability is defined as the rate and extent to which an active drug ingredient is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation at the site of action. For orally administered drugs such as rifampicin, bioavailability is influenced by several factors including drug solubility, dissolution rate, gastrointestinal absorption, metabolism, and formulation characteristics. Adequate bioavailability is essential to achieve therapeutic plasma concentrations and ensure optimal clinical efficacy[4,5].

1.2 IMPORTANCE OF RIFAMPICIN BIOAVAILABILITY

The therapeutic success of tuberculosis (TB) treatment depends not only on the intrinsic antimicrobial activity of anti-tubercular drugs but also on their pharmacokinetic properties. Among these, **bioavailability** plays a critical role in determining the rate and extent to which rifampicin reaches the systemic circulation following oral administration. Adequate bioavailability is essential to achieve therapeutic plasma concentrations required for effective bactericidal activity against *Mycobacterium tuberculosis*. Reduced bioavailability may result in subtherapeutic plasma drug concentrations, increasing the risk of treatment failure, relapse, and the emergence of drug-resistant mycobacterial strains **[4,5,9,12]**.

Several studies have demonstrated considerable variability in rifampicin exposure among patients receiving standard therapeutic doses. This variability occurs both between individuals (interindividual variability) and within the same individual over time (intraindividual variability). Factors contributing to this variability include formulation characteristics, patient demographics, body weight, disease status, genetic polymorphisms, gastrointestinal physiology, food intake, and concomitant medications. A thorough understanding of these factors is essential for optimizing dosing strategies, improving therapeutic outcomes, and minimizing the development of drug-resistant tuberculosis **[8,10,11,16,17]**.

1.2. PHARMACOKINETIC CHARACTERISTICS OF RIFAMPICIN

Rifampicin exhibits complex pharmacokinetic behavior that contributes to variability in systemic drug concentrations. According to the Biopharmaceutics Classification System (BCS), rifampicin is classified as a **Class II drug**, characterized by low aqueous solubility and high membrane permeability. Because of its limited solubility, dissolution becomes a rate-limiting step for absorption, making formulation quality a crucial determinant of bioavailability

After oral administration, rifampicin is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations typically occurring within **2–4 hours**. However, significant variation in absorption profiles has been reported among patients. Factors such as food intake, gastrointestinal function, and formulation characteristics can influence both the rate and extent of absorption **[4,5,8]**.

Rifampicin undergoes extensive hepatic metabolism, primarily through deacetylation to form **25-desacetylrifampicin**, an active metabolite that retains substantial antimycobacterial activity. Elimination occurs mainly through biliary excretion, while a smaller fraction of unchanged drug is excreted via the kidneys. The pharmacokinetics of rifampicin are nonlinear within therapeutic dose ranges due to saturation of biliary excretion pathways and dose-dependent absorption processes **[4,10,20,]**.

An important characteristic of rifampicin is its ability to induce its own metabolism, a phenomenon known as **autoinduction**. Repeated administration stimulates the expression of drug-metabolizing enzymes and transport proteins, resulting in increased clearance and reduced plasma concentrations over time. Studies indicate that most of the autoinduction effect develops within the first two weeks of therapy, leading to significant changes in drug exposure during treatment **[10,20,21]**.

1.3 FACTORS CONTRIBUTING TO PHARMACOKINETIC VARIABILITY

Substantial interindividual variability in rifampicin pharmacokinetics has been documented across diverse patient populations. Several factors have been identified as contributors to this variability **[8,10,17]**.

1.3.1 BODY WEIGHT AND DOSE ADJUSTMENT

Body weight significantly influences rifampicin distribution and clearance. To address these differences, the World Health Organization (WHO) recommends weight-banded dosing strategies. Nevertheless, variability in plasma concentrations persists even when weight-adjusted doses are used **[2,8,12]**.

1.3.2 AGE AND SEX

Demographic factors such as age and sex have been associated with differences in rifampicin exposure. Variations in body composition, hepatic function, and physiological processes may contribute to these observations **[8,10,17]**.

1.3.3 DRUG FORMULATION

Differences in manufacturing processes, excipients, and dissolution characteristics can affect the bioavailability of rifampicin-containing products. Poor-quality formulations may result in inadequate systemic exposure **[6,7,38,]**.

1.3.4 GENETIC FACTORS

Genetic polymorphisms affecting drug transporters and metabolic enzymes may alter rifampicin pharmacokinetics. Rifampicin has been identified as a substrate for transport proteins such as **P-glycoprotein (P-gp)** and **organic anion transporting polypeptide 1B1 (OATP1B1)**. Variations in the genes encoding these transporters may influence absorption, distribution, and elimination **[10,16,17]**.

1.3.5 CONCOMITANT MEDICATIONS

Drug–drug interactions can significantly affect rifampicin concentrations. Although rifampicin is a potent inducer of multiple metabolic pathways, co-administered drugs may also alter its disposition through effects on absorption or transporter activity **[5,11,16]**.

2.IMPACT OF HIV CO-INFECTION

The coexistence of HIV infection and tuberculosis presents unique therapeutic challenges. HIV-associated immunosuppression increases susceptibility to active tuberculosis and is associated with poorer treatment outcomes. Although rifampicin and many antiretroviral agents have limited direct metabolic interactions, HIV-related physiological changes may influence rifampicin pharmacokinetics **[11,16]**.

Chronic inflammation and structural alterations of gastrointestinal mucosal surfaces observed in HIV infection may affect drug absorption. Consequently, both the rate and extent of rifampicin absorption could be altered in HIV-positive individuals. Several investigations have reported lower rifampicin exposure among HIV/TB co-infected patients, whereas others have found no significant differences compared with HIV-negative patients. These conflicting findings suggest that HIV infection may contribute to pharmacokinetic variability, but the magnitude and clinical relevance of this effect remain uncertain **[8,11,17]**.

3. ROLE OF DESACETYLRIFAMPICIN

Desacetylrifampicin is the principal active metabolite of rifampicin and possesses antimicrobial activity against *Mycobacterium tuberculosis*. The metabolite contributes significantly to overall therapeutic activity and may

partially compensate for reduced parent-drug exposure in some patients. Differences in metabolite formation rates may therefore influence treatment outcomes **[4,20]**.

Understanding the relationship between rifampicin metabolism and desacetylrifampicin exposure could provide valuable insights into pharmacokinetic variability. Population pharmacokinetic studies incorporating both parent drug and metabolite measurements have suggested that variability in metabolite formation may explain part of the observed differences in systemic drug exposure. Further research is needed to determine whether specific metabolic phenotypes are associated with treatment response or risk of therapeutic failure **[20,26]**.

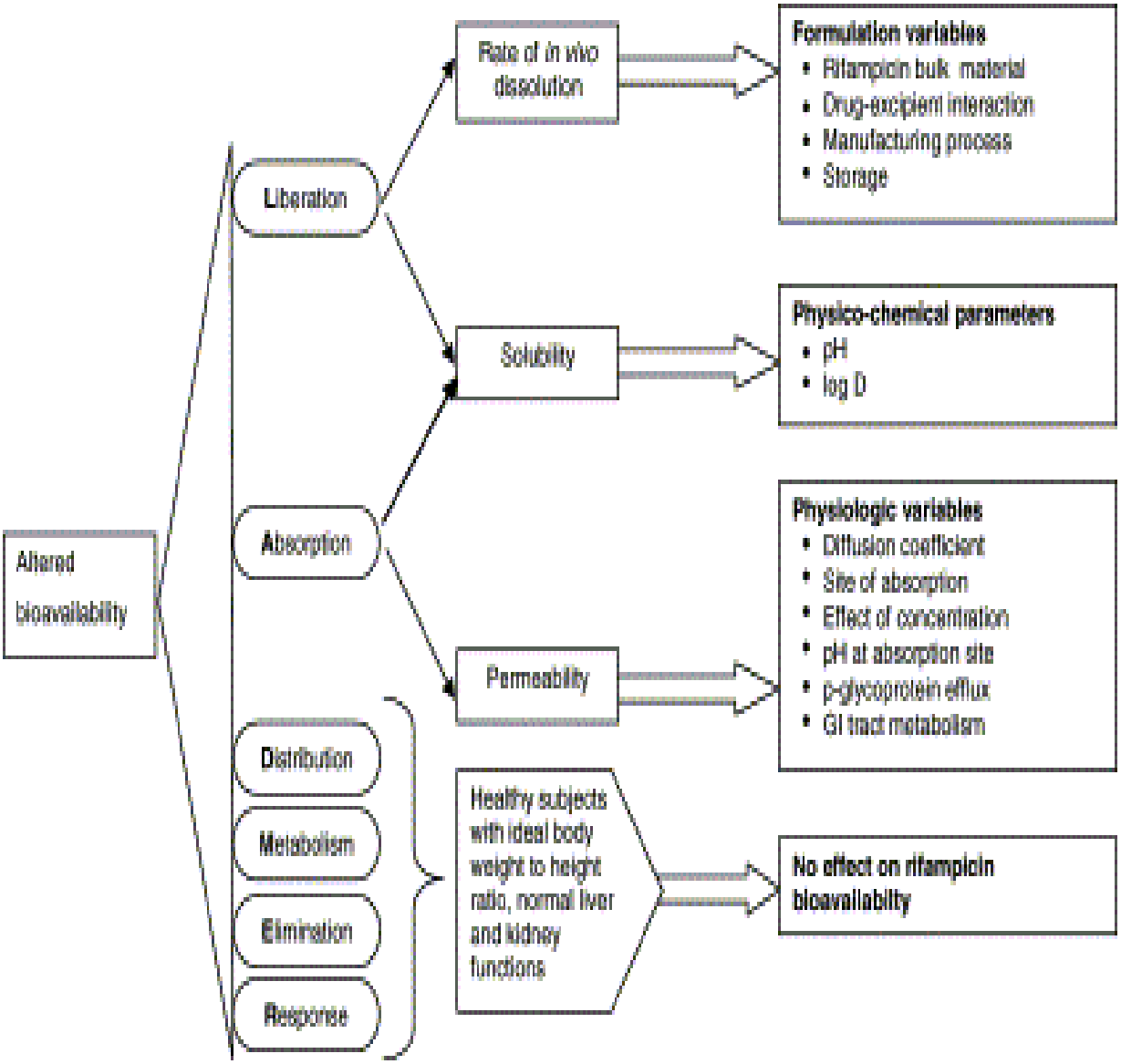
Oral Rifampicin Dose.

4. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The substantial variability in rifampicin bioavailability and pharmacokinetics has important clinical implications. Suboptimal drug exposure may contribute to delayed sputum conversion, treatment failure, relapse, and the emergence of drug-resistant tuberculosis **[9,15,17]**.

Growing evidence suggests that standard rifampicin doses may not achieve optimal therapeutic concentrations in all patients, leading to increased interest in higher-dose rifampicin regimens **[13,19,20]**.

Future strategies should focus on improving formulation quality, implementing rigorous bioequivalence standards for fixed-dose combination (FDC) products, exploring individualized dosing approaches, and utilizing therapeutic drug monitoring in selected patient populations. Population pharmacokinetic modeling and pharmacogenetic studies may further enhance understanding of factors contributing to variability and help optimize rifampicin therapy **[16,20,26]**.



5.BIOPHARMACEUTIC ASPECTS AFFECTING BIO AVAILABILTY OF RIFAMPICIN

Biopharmaceutics examines the relationship between the physicochemical properties of a drug, dosage form characteristics, and the rate and extent of drug absorption. Rifampicin exhibits considerable variability in oral bioavailability due to several biopharmaceutic factors, including poor aqueous solubility, acid instability, formulation-related issues, and food effects. These factors significantly influence therapeutic outcomes in tuberculosis treatment and may contribute to treatment failure when systemic drug exposure is inadequate.**[6,19,26,28]**

5.3.1. PHYSICOCHEMICAL PROPERTIES AND SOLUBILITY

Rifampicin is a lipophilic antibiotic with relatively poor aqueous solubility and pH-dependent dissolution characteristics. The drug exhibits different ionization states in the gastrointestinal tract, affecting its dissolution and absorption. Since dissolution is a prerequisite for absorption, limited solubility can reduce the amount of drug available for systemic uptake, leading to variability in bioavailability among patients [4,27,29]

5.3.2. DISSOLUTION CHARACTERISTICS

The dissolution rate of rifampicin is a critical determinant of its bioavailability. Factors such as particle size, crystal structure, manufacturing process, and excipient composition influence drug dissolution. Inadequate dissolution can result in reduced plasma drug concentrations and diminished therapeutic efficacy. Differences in dissolution profiles among commercial formulations have been associated with variations in rifampicin bioavailability.[19,20,27]

5.3.3. ACID INSTABILITY AND DEGRADATION

Rifampicin is chemically unstable in acidic conditions and undergoes degradation in the stomach. Under acidic pH, rifampicin can convert into 3-formyl rifamycin SV and other degradation products, reducing the amount of active drug available for absorption. This degradation process contributes significantly to variability in oral bioavailability and may be exacerbated by prolonged gastric residence time .[22,23]

5.3.4. FOOD EFFECT ON BIOAVAILABILITY

Food intake has a marked effect on rifampicin absorption. Administration with food delays gastric emptying and alters gastrointestinal conditions, leading to reduced absorption rates and lower peak plasma concentrations. Clinical studies have shown decreases in both maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) when rifampicin is administered with meals. Therefore, rifampicin is generally recommended to be taken on an empty stomach for optimal absorption .

5.3.5. DOSAGE FORM AND FORMULATION FACTORS

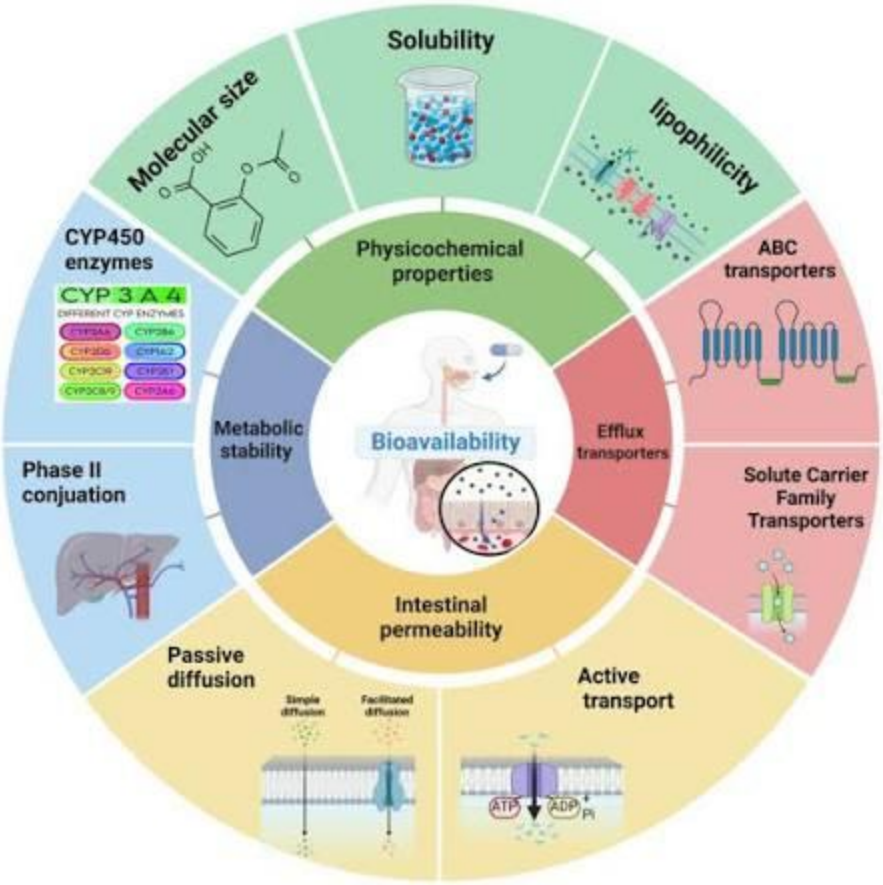
The design and composition of rifampicin dosage forms greatly influence bioavailability. Tablet hardness, granulation techniques, excipient selection, and manufacturing methods affect dissolution behavior and drug release. Variations in formulation quality have been linked to differences in therapeutic performance among rifampicin products. Careful formulation optimization is essential to ensure consistent bioavailability [20,27,32]

5.3.6. FIXED-DOSE COMBINATION (FDC) FORMULATIONS

Fixed-dose combinations containing rifampicin and isoniazid are widely used in tuberculosis treatment to improve patient adherence. However, physicochemical interactions between rifampicin and isoniazid can promote rifampicin degradation under acidic conditions. Such interactions may reduce rifampicin bioavailability and compromise therapeutic efficacy. Maintaining rifampicin stability within FDC formulations remains a major pharmaceutical challenge **[6,7,22,26]**.

5.3.7. GASTROINTESTINAL PHYSIOLOGICAL FACTORS

Gastrointestinal physiology significantly affects rifampicin absorption. Variations in gastric pH, gastric emptying rate, intestinal transit time, bile secretion, and intestinal permeability can alter the dissolution and absorption of rifampicin. Patients with gastrointestinal disorders, malnutrition, or malabsorption syndromes often exhibit reduced bioavailability and lower plasma drug concentrations [21,24]



5.3.8. DRUG–EXCIPIENT INTERACTIONS

Excipients used in rifampicin formulations can influence dissolution, stability, and absorption. Certain excipients enhance wettability and dissolution, whereas others may accelerate degradation or adversely affect drug release. Appropriate excipient selection is therefore critical during formulation development to maximize bioavailability and ensure product stability **[30,33]**

6.DRUG-RELATED FACTORS AFFECTING THE BIOAVAILABILITY OF RIFAMPICIN

Drug-related factors play a crucial role in determining the oral bioavailability of rifampicin. These factors are associated with the physicochemical properties of the drug, formulation characteristics, manufacturing processes, and dosage form design. Variations in these factors can significantly influence the rate and extent of drug absorption, leading to considerable interindividual variability in systemic drug exposure **[4,19,20,26,27]**.

6.1. SOLUBILITY OF RIFAMPICIN

Rifampicin exhibits poor aqueous solubility, which can limit its dissolution in gastrointestinal fluids. Since dissolution is a prerequisite for absorption, inadequate solubility may reduce the amount of drug available for absorption across the intestinal membrane. The solubility of rifampicin is highly dependent on pH, and changes in gastrointestinal conditions can alter its dissolution behavior and bioavailability **[4,19,21,27]**.

6.2. PARTICLE SIZE AND SURFACE AREA

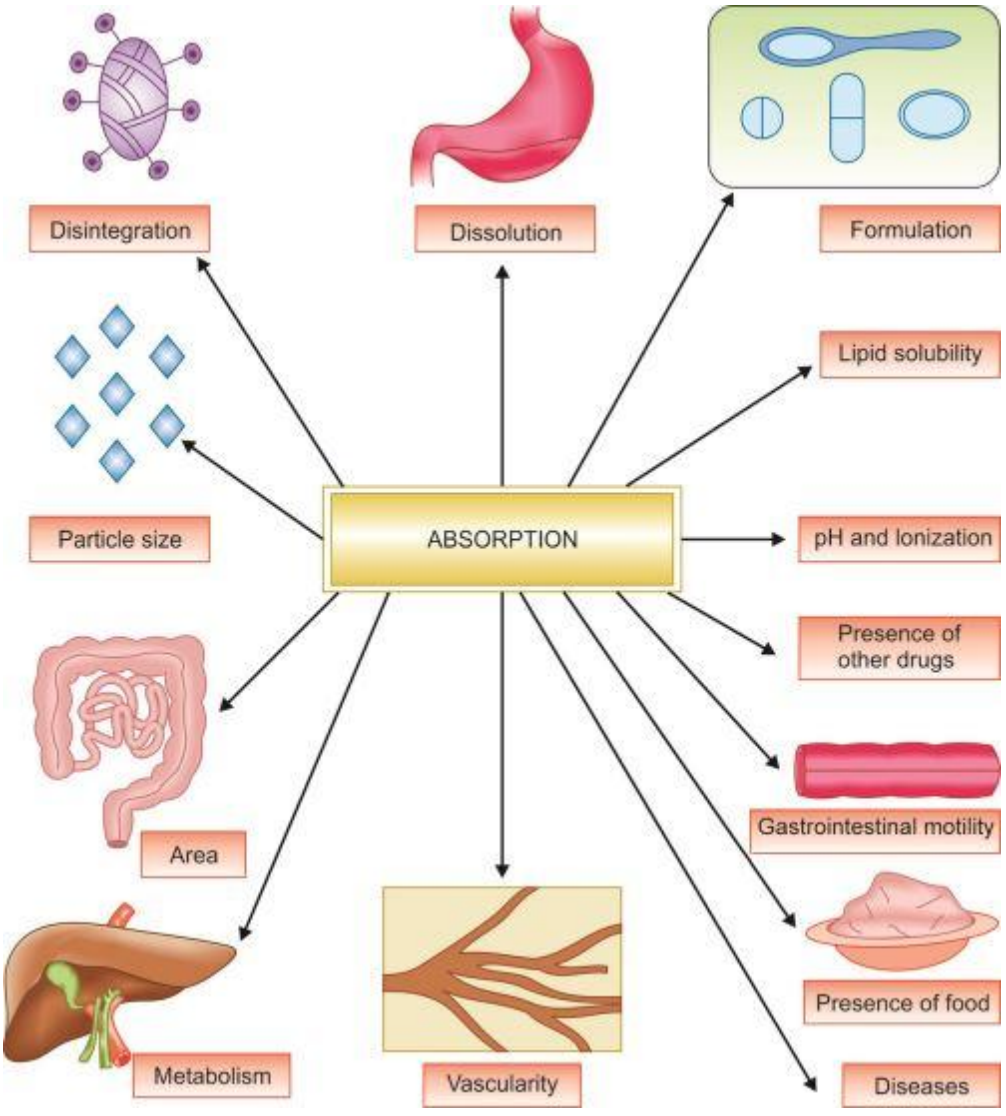
Particle size directly affects the dissolution rate of rifampicin. Smaller particles possess a larger surface area, facilitating faster dissolution and improved absorption. Conversely, larger particles dissolve more slowly, potentially resulting in reduced bioavailability. Control of particle size during formulation development is therefore essential for achieving consistent therapeutic outcomes **[20,27,28,29,31]**.

6.3. CRYSTAL FORM AND POLYMORPHISM

Rifampicin can exist in different crystalline forms that exhibit distinct physicochemical properties. Polymorphic forms may differ in solubility, dissolution rate, stability, and absorption characteristics. Changes in crystal structure during manufacturing or storage can affect the bioavailability of the final product **[20,28,29,31]**.

6.4. CHEMICAL STABILITY

Rifampicin is susceptible to degradation under acidic conditions and in the presence of moisture, heat, and certain drugs such as isoniazid. Chemical instability reduces the amount of active drug available for absorption and contributes to variability in bioavailability. Maintaining product stability throughout manufacturing, storage, and administration is therefore critical **[21,22,24,25,26]**.



6.5. EXCIPIENTS AND FORMULATION COMPONENTS

Excipients are pharmacologically inactive substances incorporated into pharmaceutical formulations to improve drug stability, manufacturability, dissolution, and patient acceptability. In rifampicin formulations, excipients play a critical role in determining drug release characteristics and maintaining chemical stability. Hydrophilic excipients such as surfactants and disintegrants can improve the wettability and dissolution rate of rifampicin, whereas certain excipients may interact chemically with rifampicin, promoting degradation or reducing its bioavailability. Therefore, careful excipient selection and compatibility studies are essential during formulation development to ensure optimal therapeutic performance **[20,22,27,31,32]**.

6.6. MANUFACTURING PROCESS

Manufacturing variables such as granulation technique, compression force, drying conditions, coating procedures, and tablet hardness can significantly influence the quality and performance of rifampicin formulations. These parameters affect tablet disintegration, dissolution rate, drug release, and ultimately systemic drug exposure. Inadequate process control may lead to batch-to-batch variability, resulting in inconsistent bioavailability and therapeutic response. Consequently, strict adherence to Good Manufacturing Practices (GMP), implementation of Quality by Design (QbD), and comprehensive quality control testing are essential to ensure consistent product quality and bioavailability **[20,25,26,30,31]**.

7. FORMULATION-RELATED FACTORS

Formulation characteristics are among the most important determinants of rifampicin bioavailability. Variations in dosage form design, manufacturing processes, excipient composition, dissolution characteristics, and product quality can significantly influence the stability, dissolution, and absorption of rifampicin. Since rifampicin exhibits poor aqueous solubility and is susceptible to degradation under acidic conditions, careful formulation development, optimization of manufacturing processes, and stringent quality control are essential to ensure consistent therapeutic efficacy **[6,19,20,25,26,31]**.

7.1 DOSAGE FORM DESIGN

Rifampicin is commercially available in several oral dosage forms, including conventional tablets, capsules, dispersible tablets, oral suspensions, and fixed-dose combination (FDC) products. The design of these dosage forms directly influences drug release, dissolution, and gastrointestinal absorption. Critical formulation variables such as particle size, tablet hardness, porosity, disintegration time, compression force, and excipient selection determine the rate and extent of rifampicin absorption. Proper optimization of dosage form design is therefore essential to achieve consistent bioavailability and therapeutic effectiveness **[6,19,20,27,31]**.

7.2BIOEQUIVALENCE ISSUES

Bioequivalence studies are essential to demonstrate that generic rifampicin formulations provide systemic drug exposure comparable to that of the innovator product. Bioequivalent formulations should exhibit similar pharmacokinetic parameters, including maximum plasma concentration (**Cmax**), time to reach maximum concentration (**Tmax**), and area under the plasma concentration–time curve (**AUC**). Regulatory agencies generally require that the 90% confidence intervals for the ratios of Cmax and AUC between test and reference products fall within accepted bioequivalence limits.

Several investigations have reported variability among generic rifampicin formulations, mainly because of differences in manufacturing practices, excipient composition, particle size distribution, and dissolution

characteristics. Consequently, rigorous bioequivalence testing, dissolution profiling, stability studies, and compliance with WHO quality standards are essential before approval and marketing of rifampicin-containing products **[7,19,25,26,30,31]**.

8. DISEASE-RELATED FACTORS

Several disease conditions can alter rifampicin absorption, metabolism, and elimination, thereby contributing to pharmacokinetic variability **[8,11,16,17]**.

8.1 HIV CO-INFECTION

HIV infection is frequently associated with gastrointestinal abnormalities, including mucosal inflammation and malabsorption, which may reduce rifampicin absorption. Several studies have reported lower rifampicin plasma concentrations in HIV/TB co-infected patients, although findings remain inconsistent across different populations **[11,16,17]**.

8.2 DIABETES MELLITUS

Patients with diabetes mellitus often experience delayed gastric emptying (gastroparesis), which can delay rifampicin absorption and reduce peak plasma concentrations. Diabetes may therefore contribute to increased pharmacokinetic variability and poorer treatment outcomes **[8,16,17]**.

8.3 GASTROINTESTINAL DISORDERS

Gastrointestinal disorders such as chronic diarrhea, inflammatory bowel disease, and malabsorption syndrome reduce intestinal drug absorption by altering gastrointestinal transit time and mucosal integrity. These conditions may significantly decrease rifampicin bioavailability

8.4 LIVER DISEASE

Since rifampicin undergoes hepatic metabolism and biliary excretion, liver dysfunction may alter drug clearance and systemic exposure. Patients with hepatic impairment require careful monitoring because altered metabolism may increase the risk of toxicity or therapeutic failure **[4,10,16]**.

9. DRUG–DRUG INTERACTIONS

Rifampicin is well known for its extensive drug–drug interaction potential because it is a potent inducer of cytochrome P450 enzymes and several drug transporters. In addition, certain co-administered medications can influence rifampicin absorption and bioavailability **[3,5,16]**.

Antacids containing aluminum hydroxide can reduce rifampicin absorption by delaying gastric emptying and decreasing drug dissolution. Therefore, rifampicin should be administered at least one hour before antacid use **[5,]**

Concomitant administration of rifampicin with antiretroviral drugs requires careful dose adjustment because rifampicin markedly induces hepatic enzymes involved in the metabolism of many HIV medications, potentially reducing their therapeutic efficacy **[3,11,16]**.

Proton pump inhibitors may alter gastric pH and influence rifampicin dissolution, although their overall clinical impact appears limited compared with food effects **[5,16]**.

Interactions with other anti-tuberculosis drugs, particularly isoniazid in fixed-dose combination products, may reduce rifampicin stability under acidic gastric conditions and decrease its bioavailability **[6,]**.

10. PHARMACOKINETIC VARIABILITY

Rifampicin exhibits substantial pharmacokinetic variability among patients receiving standard therapeutic doses. This variability influences plasma drug concentrations and may affect treatment efficacy and safety. Differences in absorption, distribution, metabolism, and elimination result in considerable variation in systemic exposure despite administration of the same dose. Several patient-related, disease-related, formulation-related, and genetic factors contribute to this variability, making it difficult to achieve optimal drug concentrations in every individual. Understanding the determinants of pharmacokinetic variability is essential for optimizing rifampicin therapy and improving tuberculosis treatment outcomes [4,8,10,16,18]**.**

10.1.CLINICAL IMPLICATIONS

Subtherapeutic rifampicin concentrations reduce bactericidal activity against *Mycobacterium tuberculosis* and are associated with delayed sputum culture conversion, prolonged infectiousness, treatment failure, relapse, and the emergence of rifampicin-resistant and multidrug-resistant tuberculosis **[9,12,15,17]**.

Maintaining adequate rifampicin exposure is therefore essential for maximizing treatment success and preventing the development of antimicrobial resistance **[1,2,9]**.

10.2 INTERINDIVIDUAL VARIABILITY

Interindividual variability refers to the differences in pharmacokinetic parameters observed between different patients receiving the same rifampicin dose. Such variability is influenced by body weight, age, sex, nutritional status, genetic polymorphisms, liver function, gastrointestinal physiology, concomitant diseases, and co-administered medications. Variations in formulation quality and drug absorption further contribute to differences in plasma rifampicin concentrations. Consequently, some patients may achieve therapeutic drug exposure, whereas others remain below the desired concentration despite receiving standard weight-based doses **[8,10,12,16]**.

10.3Intraindividual Variability

Intraindividual variability describes changes in rifampicin pharmacokinetics within the same patient during the course of treatment. Plasma drug concentrations may fluctuate because of alterations in gastrointestinal function, disease progression, nutritional status, medication adherence, or changes in hepatic enzyme activity. One of the most important contributors to intraindividual variability is rifampicin-induced autoinduction, which progressively increases drug clearance during the initial weeks of therapy. Monitoring these changes is important when interpreting pharmacokinetic measurements obtained at different stages of treatment **[4,10,18]**.

10.4Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring involves measuring rifampicin plasma concentrations to determine whether therapeutic exposure has been achieved. TDM is especially useful in patients who exhibit poor clinical response, delayed sputum conversion, HIV co-infection, diabetes mellitus, gastrointestinal disorders, or suspected malabsorption. Individualized dose adjustment based on measured drug concentrations can help achieve optimal exposure while reducing the risk of treatment failure and toxicity. Although routine TDM is not recommended for all patients, it is increasingly recognized as a valuable tool in selected clinical situations **[5,15,16]**.

10.5Autoinduction

A distinctive characteristic of rifampicin is its ability to induce its own metabolism, a process known as **autoinduction**. Following repeated administration, rifampicin stimulates hepatic drug-metabolizing enzymes and transport proteins, leading to progressive increases in drug clearance and corresponding reductions in plasma concentrations. Most of the autoinduction effect develops during the first one to two weeks of therapy. This phenomenon should be considered when interpreting pharmacokinetic data and designing individualized dosing strategies **[4,12,18]**.

10.6Area Under the Concentration–Time Curve (AUC)

The area under the plasma concentration–time curve (**AUC**) represents the total systemic exposure to rifampicin over time. Unlike Cmax, which reflects peak exposure, AUC provides an overall measure of the extent of drug absorption. Low AUC values indicate insufficient drug exposure and have been associated with reduced treatment efficacy, slower sputum conversion, and increased risk of relapse. Assessment of AUC is widely used in pharmacokinetic studies evaluating rifampicin bioavailability and dose optimization strategies **[9,13,17,18]**.

10.7Clearance

Drug clearance is defined as the volume of plasma from which rifampicin is completely removed per unit time. Clearance is primarily determined by hepatic metabolism and biliary excretion. Factors such as liver function, body weight, genetic variability, and enzyme induction influence rifampicin clearance. Increased clearance results in lower plasma drug concentrations and reduced systemic exposure, whereas decreased clearance may increase the risk of adverse effects. Understanding clearance variability is essential for selecting appropriate dosing regimens in different patient populations **[4,10,18]**.

11. STRATEGIES TO IMPROVE RIFAMPICIN BIOAVAILABILITY

Several strategies have been proposed to improve the oral bioavailability of rifampicin. These include optimizing formulation design, improving the quality and stability of fixed-dose combination (FDC) products, implementing rigorous bioequivalence testing, and ensuring compliance with Good Manufacturing Practices (GMP). Advanced formulation approaches such as optimization of particle size, selection of suitable excipients, enhancement of dissolution characteristics, and maintenance of chemical stability are essential to achieve consistent systemic drug exposure and therapeutic efficacy **[6,19,20,25,26,30,31]**.

Therapeutic drug monitoring (TDM) has emerged as an important strategy for identifying patients with subtherapeutic rifampicin concentrations and guiding individualized dose adjustment. TDM is particularly beneficial in patients with HIV co-infection, diabetes mellitus, gastrointestinal disorders, malabsorption syndromes, or poor clinical response to standard therapy. Individualized dosing based on plasma drug concentrations may improve treatment success while minimizing the risk of toxicity and the development of drug resistance **[5,15,16]**.

Recent clinical studies have demonstrated that higher rifampicin doses (20–35 mg/kg) produce substantially greater systemic drug exposure, including increased peak plasma concentrations (Cmax) and area under the concentration–time curve (AUC), compared with the conventional 10 mg/kg dose. These higher doses have shown enhanced early bactericidal activity and may shorten treatment duration without causing a clinically significant increase in serious adverse effects in carefully selected patients. However, additional large-scale clinical trials are needed to establish the long-term safety and efficacy of high-dose rifampicin therapy **[12,13,17,18]**.

Emerging drug delivery technologies have shown considerable promise for improving rifampicin bioavailability. Nanoparticle-based formulations, liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, nanoemulsions, self-emulsifying drug delivery systems (SEDDS), and cyclodextrin inclusion complexes have been investigated to enhance rifampicin solubility, protect the drug from degradation in the gastrointestinal tract, and improve intestinal absorption. Although many of these technologies remain under development, they represent promising strategies for future tuberculosis therapy **[20,26,27,30]**.

Furthermore, personalized medicine approaches incorporating pharmacogenetic testing, population pharmacokinetic (PopPK) modeling, and model-informed precision dosing (MIPD) may enable individualized rifampicin therapy. These approaches consider patient-specific factors such as body weight, age, genetic polymorphisms, disease status, and concomitant medications to optimize drug exposure and improve treatment outcomes **[10,16,18]**.

11.CONCLUSION

Rifampicin remains the cornerstone of first-line anti-tuberculosis therapy because of its potent bactericidal activity against *Mycobacterium tuberculosis* and its ability to shorten treatment duration. However, considerable interindividual variability in rifampicin bioavailability and pharmacokinetics continues to present a major challenge in achieving optimal therapeutic outcomes. This variability is influenced by multiple factors, including physicochemical properties, formulation quality, fixed-dose combination (FDC) products, manufacturing processes, patient-related characteristics such as body weight, age, nutritional status, and genetic polymorphisms, as well as disease conditions, concomitant medications, and rifampicin autoinduction **[2,4,6,8,10,12,16,19,20,26]**.

Clinical and pharmacokinetic studies have demonstrated that inadequate rifampicin exposure is associated with delayed sputum conversion, treatment failure, relapse, and the emergence of multidrug-resistant and rifampicin-resistant tuberculosis. Therefore, ensuring the quality, stability, and bioequivalence of rifampicin-containing formulations is essential for maximizing therapeutic efficacy and minimizing the risk of drug resistance **[5,7,9,15,17,25]**.

Recent advances in population pharmacokinetic modeling, therapeutic drug monitoring (TDM), and individualized dose optimization have improved the understanding of rifampicin pharmacokinetic variability and support more personalized treatment strategies. In addition, growing evidence indicates that higher rifampicin doses may safely increase systemic drug exposure and enhance treatment outcomes in selected patient populations when administered under appropriate clinical supervision **[13,15,17,18]**.

Future research should focus on the development of high-quality and innovative drug delivery systems, incorporation of pharmacogenomic information into clinical practice, application of model-informed precision dosing, and optimization of fixed-dose combination formulations. These approaches have the potential to improve rifampicin bioavailability, achieve consistent therapeutic drug concentrations, and enhance tuberculosis treatment outcomes across diverse patient populations **[16,18,20,26,27,30,31]**.

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