

Review

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Review

Filling the Void in Pediatric Tuberculosis Treatment: Challenges and the Promise of Rifampicin Self-Emulsifying Drug Delivery Systems

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Abstract

Tuberculosis (TB) persists as a devastating global health crisis, exacting a disproportionate burden on low-middle-income countries (LMIC), within which the burgeoning pediatric TB population is especially vulnerable to severe TB manifestations. Rifampicin, a cornerstone of the first-line TB regimen, is indispensable; yet its therapeutic potential is substantially constrained by intrinsic poor aqueous solubility, limited permeability, physicochemical instabilities, and deleterious drug-drug interactions with drugs such as isoniazid. Although current research focuses on formulating rifampicin into fixed-dose combinations – some reporting improved outcomes – the variable and often suboptimal rifampicin bioavailability in such formulations remains a critical concern. Consequently, the development of a stable, independent rifampicin oral formulation should be prioritized to ensure effective TB treatment. There are currently no commercially available rifampicin-only liquid preparations, despite the urgent need for palatable, flexible, age-appropriate formulations. This paucity constitutes a profound and persistent gap in pediatric TB, compromising accurate weight-based dosing, treatment adherence, and therapeutic outcomes while contributing to rifampicin resistance. This paper highlights the key characteristics and formulation challenges of rifampicin, with particular emphasis on pediatric TB. It further discusses liquid self-emulsifying drug delivery systems (SEDDS) as a novel approach to enhance oral rifampicin delivery. These feasible lipid-based delivery systems offer notable promise, as they are capable of maintaining rifampicin in a solubilized and stable state throughout the gastrointestinal tract, which in turn will likely improve bioavailability. The possible development of a stable liquid rifampicin SEDDS represents a paradigm shift in addressing the longstanding neglect of pediatric TB treatment.

Keywords: lipid-based drug delivery system; oral administration; pediatric tuberculosis; rifampicin; physicochemical instabilities; self-emulsifying drug delivery system (SEDDS)

1. Introduction

Tuberculosis (TB) remains a dynamic and devastating global health crisis firmly ingrained in persistent multifaced socioeconomic inequities [1–6], including the denial of basic human rights, systemic neglect, and socioeconomic disparities [1,3,7]. In fact, this disease imposes a disproportionate burden on low- and middle-income countries (LMICs), which account for more than 95% of global TB occurrences and morbidity cases [5,8,9], as will be elaborated on further below. Moreover, despite endeavors to eradicate TB [8,10], a disease caused by various strains of *Mycobacterium tuberculosis* [11–14], it has reclaimed its grim title as the 'world's leading cause of death' due to a single infectious organism [5,8,15]. Indeed, with shortcomings in currently available pharmacological treatment strategies, significant scientific challenges remain for drug discovery, treatment strategies, refinement and optimization of drug formulations, all warranting further investigation and developments.

The World Health Organization (WHO) estimates that approximately 10.8 million people developed TB in 2023 alone, with a concerning 1.3 million cases occurring in the pediatric population [8]. Throughout history, pediatric TB has been neglected or overlooked, primarily because of the misperception that children are minor contributors to the global epidemic, predominantly given their lower TB infection incidence relative to that of adults, and the assumption that children seldom develop severe forms of TB [16,17]. In fact, children under the age of five years are at higher risk of developing severe or fatal active forms of TB compared to older pediatric patients [4,18–20]. Furthermore, without appropriate testing and treatment of exposed children, a silent biological reservoir of TB infection could persist. This could lead to TB cases resurfacing in future, thereby undermining global TB control and eradication efforts [4,16].

Emerging evidence indicates that, similar to adults, pediatric pulmonary TB survivors remain vulnerable to the long-term consequences associated with TB, such as post-tuberculosis lung disease, which causes lasting respiratory impairment [21–24]. This is especially concerning for pediatric patients due to their longer anticipated remaining lifespan [24]. Moreover, malnutrition, erratic treatment compliance, as well as inaccurate and subtherapeutic rifampicin doses can lead to drug resistance and treatment failure in children suffering from active TB [17,25,26]. Drug-resistant pediatric TB often requires prolonged treatment and increases the susceptibility to lung damage [21,24,27]. As a result, TB can profoundly affect young people, disrupting their education, development, and future economic prospects [28].

Currently, chemotherapy remains the only viable and effective clinical treatment option for TB patients [29]. Anti-TB drugs often exhibit poor therapeutic profiles, including poor bioavailability due to undesirable first-pass metabolism and variable drug absorption [29–32]. Among these therapeutic limitations associated with effective TB treatment regimens are the toxicity of individual and combined drugs, drug interactions, lengthy treatment regimes, as well as severe adverse drug reactions [29,33–36] that consequently also contribute to the emergence of multi-drug resistant strains, treatment failure, and poor patient adherence [29].

Rifampicin, a frontier drug in the first-line anti-TB regimen, is often incorporated with isoniazid, pyrazinamide, and ethambutol in fixed-dose combination therapy, such as tablets and oral dispersible tablets [8,37,38]. However, this drug is thermally unstable and exhibits increased degradation when exposed to acidic conditions and/or when co-formulated with isoniazid [30,39–41]. Consequently, current pediatric fixed-dose combination therapy often results in suboptimal rifampicin therapeutic levels [25,42]. Moreover, since ample water is required for the effective delivery of pediatric dispersible tablets [37], restricted access to clean and safe water poses yet another notable treatment barrier in resource-limited countries.

Furthermore, pediatric TB treatment regimens are usually extrapolated from adult treatment regimens and are adjusted according to the age and weight of the child, to compensate for the developmental, physiological, and pharmacodynamic differences between children and adults [17,43,44]. From a pharmacological perspective, children are not merely “small adults”. They often display qualitative and quantitative differences in pharmacodynamics and pharmacokinetics, and therefore simple extrapolations from adult data frequently fail to produce child-appropriate formulations or optimal drug dosing [37]. Research has also reported that the majority of commercially available drug products prescribed for pediatric TB patients are not suitable dosage forms for pediatric consumption [17,45–49]. In South Africa, a region with a high TB burden, only two rifampicin-containing dosage forms, namely capsules and vials, are currently registered and commercially available for adult use. Added to that, these may not necessarily be readily available, particularly following a recent discontinuation of the only rifampicin oral suspension [8,50]. Thus, the lack of child-appropriate dosage forms often necessitates reconstitution into extemporaneous formulations [51].

Despite the clinical need for commercially available liquid formulations of rifampicin, such products remain scarce due to the challenging physicochemical properties of rifampicin and the niche market for pediatric use [51]. This exposes a significant gap in pediatric TB treatment. Effective

pediatric TB treatment requires age-appropriate formulations carefully designed to ensure efficient and safe drug delivery and pharmacotherapy [52,53].

The persistent challenges with rifampicin prompt a fundamental question: Can the stability of rifampicin in liquid formulations be adequately improved via science and innovation? Addressing this gap is imperative to meet the clinical needs of pediatric TB patients around the world.

2. Pediatric Tuberculosis

As stated above, pediatric TB constitutes a significant yet underprioritized global health concern, where preventable morbidity and mortality among the most fragile age groups persist. In fact, epidemiological data suggest that the global pediatric TB distribution mirrors that of adults [4], with a substantial disease burden in Africa and Southeast Asia, accounting for 80% of global HIV-negative TB-related deaths [8]. It is worth noting that five countries — China, India, Indonesia, Pakistan, and the Philippines — account for more than half of all the TB cases globally [8]. In 2023, the WHO reported that children under 15 years old make up approximately 12% of the estimated total TB incident cases; however, despite this lower incidence, they represent 15% of the projected global TB mortality [8]. These reported statistics on the global pediatric TB burden may not reflect the full picture, as most cases often go unreported or undiagnosed, and as such, the true global numbers may be considerably higher [8,16]. In most high-burden regions, TB deaths are often attributed, without a confirmed diagnosis, to meningitis or pneumonia — common causes of death among children under five years, especially in LMICs [16,17,54,55]. Moreover, diagnosing pediatric TB patients is known to be especially challenging, given the different clinical manifestations, the paucibacillary nature of TB, clinical resemblance with other pediatric diseases [4], age-related and non-specific symptoms, gaps in diagnosis, and limited access to treatment and diagnostic services, especially for children under the age of 15 years [55–57]. Pediatric TB screening and diagnostic methods include culture, smear microscopy, nucleic acid amplification assays, tuberculin skin test, and imaging [55,58]. However, these techniques are limited by challenges in obtaining quality specimens, low bacterial loads, and decreased test performance in immunocompromised or young children. As a result, there is no single diagnostic test that can rapidly, accurately, and reliably detect pediatric TB [55,58]. Without accurate estimates of the global pediatric TB burden, resources for treatment, diagnosis, and the demand for new drug development will be inadequately allocated, which in turn diminishes the incentive of pharmaceutical industries to prioritize the development of anti-TB drugs. Collectively, these factors are crucial to advocate for and manage pediatric TB, initiate timely treatment, and prevent fatalities [57,59].

2.1. Pediatric Tuberculosis Transmission and Disease Progression

Mycobacterium tuberculosis, complex intracellular organisms, such as *M. canetti*, *M. bovis* BCG, *M. bovis*, *M. africanum* (along with other species and strains that are rarely pathogenic to humans), are transmitted through the respiratory route when minute infected droplets are aerosolized from pulmonary or laryngeal TB patients, followed by inhalation into the lungs of close contacts [55,60,61]. The risk of TB infection and progression after a primary *M. tuberculosis* infection is greatly influenced by the immunologic function and age of the patient [62,65]. Accordingly, the guideline on clinical investigation of medicinal products in the pediatric population (CHMP/ICH/2711/99) categorizes pediatric age groups based on developmental changes as follows: preterm newborn infants; term newborn infants (0–27 days); infants and toddlers (1 months to 23 months); children (2–11 years), subdivided into pre-school children (2–5 years) and school children (6–11 years), and ultimately adolescents (12–16 or 18 years), with the applicable classification depending on regional definitions [66].

Furthermore, child-to-child TB transmission is rare [60,63,67]. In fact, cavitary forms of TB are less frequent in children, except for those with genetic immune response modifications or HIV [60]. Therefore, TB transmission among pediatrics is often due to close and prolonged exposure to adults with infectious pulmonary TB [4,17]. It is worth noting, however, that pediatric TB follows a bimodal

risk profile. The highest transmission risks are observed in children under two years of age and in late adolescence, whereas the risk for children aged between five and ten years is considerably lower [64,67]. Since children under two years depend extensively on adult supervision, they usually contract TB from close household members [65,67], whereas older children, being more independent and socially active, often acquire TB infection from an external source [17,68]. Adults receiving regular and appropriate treatment for pulmonary TB seldom infect children; however, the greater risk lies with those having chronic TB that remains undiagnosed, relapse due to drug resistance, or when inadequately treated [67].

Regarding disease progression, children under two years of age or with impaired immunological response facilitate persistent replication of mycobacteria and their progression to pulmonary disease or its dissemination to other physiological regions [60,65]. Conversely, similar to the risks of contracting TB mentioned above, the risk of disease progression is low in children aged five to ten years, whereas adolescents are more susceptible to disease reactivation [69]. The age-related risk of TB progression is shown in Figure 1 [64].

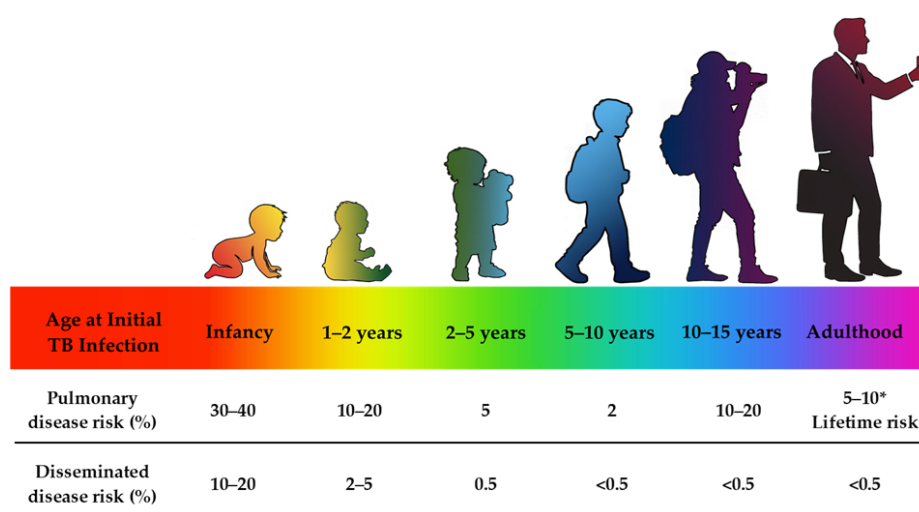


Figure 1. Age-related risk of TB development after initial infection prior to the chemotherapy era. Adapted from [55,64].

Moreover, numerous factors contribute to the transition from pediatric TB infection to active disease and the severity thereof, including the virulence of the mycobacterium strain, the burden of mycobacterial exposure, and the time since exposure, during which the first two post-exposure years coincide with the highest risk [55]. In addition, disease progression is influenced by environmental and host risk factors encompassing immunocompromising status (including HIV/AIDS, chronic renal disease, and the use of immunosuppressants such as chemotherapy for malignancy), environmental exposures to indoor air pollutants and tobacco smoke, and socioeconomic conditions, comprising overcrowding living conditions, and malnutrition [55,70,71].

2.2. Clinical Manifestation of Pediatric Tuberculosis

Following exposure, the pathogen is either eliminated or persists within the body; consequently, its persistence may result in a latent or active TB infection [60]. Latent or dormant TB refers to a non-replicating state of the pathogen, occurring without active disease manifestations and symptoms [56] and which may persist for years until reactivation. The risk of a healthy adult with a latent TB infection developing active TB is 5–10% over their lifetime, with a higher likelihood of progression to TB within the first two years after primary infection [69]. Compared to adults, infants with a latent TB infection have a 5–10 times greater probability of developing active TB and are at greater risk of severe disseminated manifestations [4,18–20]. Moreover, with proper management, such as prompt

initiation of treatment with appropriate drug dosages, pediatric treatment outcomes are generally favorable [55]. This, however, highlights a troubling reality that, despite TB being a preventable and generally curable disease [8], the most vulnerable groups continue to bear the greatest burden of neglect.

Pulmonary TB, a lung-localized infection, remains the most prevalent form in the overall pediatric population, with marginal interindividual variation in age-dependent symptom severity [4]. Approximately 50% of infants exhibit systemic or respiratory symptoms during the primary phase of TB, whereas up to 90% of newly infected older children will remain asymptomatic [72]. Younger children often present with symptoms such as cough, chills, fever, enlarged lymph nodes, weight loss, and stunted growth. Manifestation in adolescents, on the other hand, often resembles adult-type TB and tends to have slightly different signs and symptoms, including chest pain, prolonged cough, night sweats, chills, fever, fatigue, weakness, hemoptysis, anorexia, enlarged lymph nodes, and weight loss [67].

Extrapulmonary: TB accounts for 20–30% of all pediatric TB cases [73]. The clinical presentation varies according to the site of infection, and these sites may include, but are not confined to, the lymph nodes, pleura, abdomen, cutaneous, musculoskeletal system, the cardiac system, meninges, and widespread or miliary dissemination [74]. Notably, the type and severity of extrapulmonary TB in pediatric patients are largely determined by host-pathogen interactions, which often present differently among this diverse age group [17]. Following, several manifestations of pediatric extrapulmonary TB infection are described next.

2.2.1. Indications of Pediatric Extrapulmonary Tuberculosis Infection

The most prevalent type of extrapulmonary TB among children aged 2 to 10 years is *TB lymphadenitis* [74,75]. Lymph nodes localized in the neck are usually affected; however, lymph node involvement of the axillary, abdominal, supraclavicular, and thoracic regions may also occur [17]. Clinically, it presents as asymmetrical, non-tender, painless lymph node enlargement for more than a month, with or without a discharging sinus, and presents predominantly in the neck [74].

Occasionally, pediatric patients may develop *pleural TB*, sometimes without pulmonary lesions [74]. Typical clinical presentation in these cases includes reduced breath sounds and dullness on percussion, with or without chest pain [74].

Young children are not often diagnosed with *abdominal TB*, but this form accounts for about 12% of extrapulmonary TB cases in children under 15 years, with increased susceptibility in children aged five and older [74], representing approximately 1–3% of all TB cases [76]. Abdominal TB typically presents with non-specific symptoms [76,77], but may entail abdominal swelling with abdominal masses or ascites [74]. The most prevalent forms among children are adhesive peritonitis or nodal disease, of either the fibrotic or the wet type, whereas gastrointestinal-involved extrapulmonary TB is more common in adults [77].

Although *cutaneous TB* accounts for only 1–2% of all TB infections, a considerable number of these cases occur in children aged 10 to 14 years [17]. In younger children, this type of TB often involves systemic organs and lymph nodes, with scrofuloderma (i.e., cutaneous manifestation) as the most prevalent form of this disease [17]. Diagnosing the latter in the pediatric population is challenging due to its variable and non-specific presentation, including both multibacillary and paucibacillary forms [17].

Osteoarticular TB is uncommon in the pediatric population [78], however, infants can still occasionally develop this disease. Most cases occur in children older than five years. Osteoarticular TB symptoms often include unilateral knee or hip effusion and limited movement due to swelling at the ends of long bones. Notably, because of painful joints or limbs and limping, osteoarticular TB is often misattributed to trauma [63,74]. *Spinal TB*, known as Pott's spine, accounts for 50% of all osteoarticular TB cases. It primarily affects children aged five years and older; though younger children tend to develop more severe deformities [63,74,78,79]. Spinal TB typically presents with spine deformity, lower limb weakness/inability to walk, or paralysis [63,74,79]. Apart from spinal TB that

typically affects young children, *skeletal TB* usually occurs within the first two decades of life and accounts for 10–20% pediatric extrapulmonary TB cases [80]. As children grow, their transphyseal vessels start to diminish, rendering eighteen-month-old children and younger more prone to develop *TB arthritis* [81].

Infection of the cardiac system, i.e., *pericardial TB*, is rare, accounting for less than 4% of the cases [82]. The pericardial tissue is the most frequently infected site, presenting either as a normal TB infection or leading to pericardial effusion and pericarditis, which may subsequently cause hemodynamic effects [74,79]. Typical signs include distant heart sounds, cardiac failure, and difficulty palpating the apex beat [74].

TB meningitis, which is an extrapulmonary TB presentation with central nervous system involvement, is the deadliest and most debilitating form of tuberculosis that disproportionately targets young children, especially children under five with disseminated TB, as well as those with advanced or life-threatening diseases [74]. Despite treatment, mortality rates range from 15% to 40%, and over one-third suffer lasting or permanent neurological defects [4,83]. Typical clinical presentations include headache, neck stiffness, irritability or abnormal behavior, lethargy or reduced consciousness, vomiting (in the absence of diarrhea), convulsions, cranial nerve palsies, and bulging fontanelle [74].

Miliary TB, on the other hand, is a severe, life-threatening form of disseminated TB, resulting from an extensive lymphohematogenous distribution of the pathogen from the primary TB infection site [84]. The typical clinical presentation entails: non-specific, persistent fever, and lethargy [74], and may resemble those of other common pediatric diseases, depending on which specific organs are involved [84]. The most affected groups are usually the terminally ill and children under five with disseminated TB [74].

3. Therapeutic Management of Pediatric Drug-Susceptible Tuberculosis

3.1. Current Treatment of Drug-Susceptible Pediatric Tuberculosis

The goal of pediatric TB treatment is to prevent TB infection from progressing to active TB and to reduce the reservoir for future TB incidents [69]. The principles of TB treatment are mostly consistent between adults and children; however, in pediatric patients, weight-based dosing is required for all drugs due to pharmacokinetic differences within the pediatric population, as well as differences between children and adults [4,43,44,74,85]. The selection of TB regimens for pediatric patients is further influenced by various factors such as the age of the pediatric patient, the severity of the disease, comorbidities, HIV status, antiretroviral therapy, and the affordability and availability of child-friendly formulations [18,69,86].

In general, drug-susceptible pediatric TB, without suspicion or confirmation of drug resistance, is treated with a combination of antitubercular drugs, usually available in fixed-dose combinations, over a typical period of six months consisting of an intensive and a continuation phase. Though, the regimen and duration may be adjusted if drug resistance is present [87,88]. The standard regimen recommended for drug-susceptible TB includes a 'three/four-drug cocktail' comprising isoniazid, rifampicin, pyrazinamide, with or without ethambutol [8,86,89].

During the intensive TB treatment phase, the drugs used are predominantly bactericidal, rapidly eliminating substantial amounts of pathogenic bacteria and thereby preventing TB progression, transmission, and the development of drug resistance [88,89]. The drugs involved in the continuation phase are sterilizing agents that eradicate intermittently active or dormant bacilli, which often results in complete bacterial eradication, successful TB treatment, and the prevention of disease relapse [88,89]. Both rifampicin and isoniazid serve as the indispensable cornerstones for both treatment phases, whereas pyrazinamide and ethambutol are usually incorporated depending on various patient-specific factors [17,88].

When pediatric patients transition from the intensive phase to the continuation treatment phase, which typically involves two drugs administered multiple times per week rather than daily, directly

observed therapy, if required or available, can be an effective supporting strategy to improve adherence in children [4]. The preferred pediatric pulmonary TB treatment, particularly for patients at a high risk of isoniazid resistance, with extensive pulmonary TB, and/or living in areas of high HIV prevalence, is the four-drug regimen. Ethambutol is included to provide additional protection against the development of resistance in cases of high bacterial load [85].

In contrast, the three-drug treatment regimen, which excludes ethambutol, is preferred for pediatric patients with confirmed or suspected pulmonary TB who reside in regions with low HIV prevalence, where HIV negative status is associated with minimal risk of isoniazid resistance [85]. The WHO Module 5 outlines the current pediatric treatment regimens for both TB infections and drug-susceptible TB, covering presentations from non-severe to severe [86]. A summary of these regimens is provided in Table 1.

Table 1. A summary of pediatric TB treatment regimens for TB infection, as well as drug-susceptible TB, including non-severe and severe TB [63,69,86].

Type of TB Regimen	Drugs	Durati on (mont hs)	Recommended Regimen	Key Consideration
Tuberculosis Infection	Isoniazid (H) Rifampicin (R)	3	All pediatric patients. Preferred for HIV-negative children <25 kg.	Use dispersible fixed dose combinations if available. Vitamin B6 supplements for selected patients.* No pediatric-friendly formulation is readily available: In adolescents and older children, a rifampicin tablet may be used; compounding or tablet crushing may be necessary for younger children. Use if suspected or resistance to isoniazid.
	Rifampicin (R)	4	All pediatric patients.	Use if rifampicin is contraindicated or not available. Vitamin B6 supplements for selected patients.*
	Isoniazid (H)	6 or 9	All pediatric patients. Preferred for HIV-positive children on anti-retroviral therapy.	Administer with fatty food. Vitamin B6 supplements for selected patients.*
	Isoniazid (H) Rifapentine (P)	3	≥2 years. This regimen is not recommended for HIV-positive children.	
Non-severe drug-susceptible TB	2HRZE/2HR Isoniazid (H) Rifampicin (R) Pyrazinamide (P) ±Ethambutol (E)	4	Pediatric patients ≥3 months to <16 years with non-severe peripheral lymph node or pulmonary TB.	Meets WHO non-severe TB criteria (uncomplicated pleural effusion; non-cavitary, paucibacillary disease. Confined to one lung lobe without miliary pattern; intrathoracic lymph node TB without airway obstruction). Ethambutol optional. Exclude rifampicin

				resistance. Child-friendly formulations available.
Severe drug-susceptible TB	2HRZE/4HR	Isoniazid (H) Rifampicin (R) Pyrazinamide (P) ±Ethambutol (E)	6	All pediatric patients with severe TB. Include severe pulmonary TB (cavitary, extensive, and miliary TB) and all forms of extrapulmonary TB, except osteoarticular TB and TB meningitis. Ethambutol should always be included in the intensive phase. Child-friendly dispersible formulations available.
Osteoarticular TB and meningitis	2HRZE/10HR	Isoniazid (H) Rifampicin (R) Pyrazinamide (P) ±Ethambutol (E)	12	All pediatric patients with osteoarticular TB or TB meningitis. For osteoarticular TB, consider surgical intervention if needed and focus on adherence. For TB meningitis, consider high rifampicin dosages to achieve optimal central nervous system penetration. Add corticosteroids. Initiate treatment in hospital. Monitor for neurological and hepatotoxicity changes. Child-friendly formulations available.

* The selected patients for Vitamin B6 supplementation include infants who are exclusively breastfed, children, and adolescents with milk- or meat-deficient diets, malnourished pediatric patients, and symptomatic HIV-positive children. Completing the prescribed TB regimen is crucial, as interruption or incorrect use can result in disease recurrence, drug resistance, as well as prolonged, more costly, or even failed treatment [90]. Moreover, determining the optimal TB antibiotic dose to achieve effective systemic drug levels – thereby minimizing toxicity while maximizing the therapeutic efficacy – within the pediatric population is often a formidable challenge due to low drug serum concentration and poor patient treatment adherence [17,37]. This frequently leads to unsuccessful treatment and the emergence of drug-resistant strains, which are considerably more challenging to manage [17]. Furthermore, TB management during this stage of disease is more arduous due to the more extended treatment period, higher costs compared to first-line treatment, and the necessity for injectable drugs; all of which contribute to poor patient adherence and increased severity of side effects [17].

3.2. General Classification of First-line Antitubercular Drugs

First-line antitubercular drugs that include isoniazid, rifampicin, and pyrazinamide, with or without ethambutol, are commonly used to treat drug-susceptible TB [8,86]. Their pharmacological properties and use are described below.

Isoniazid, also known as isonicotinic acid hydrazide, is a prodrug that is converted to its active metabolite by the enzyme catalase-peroxidase [91,92]. This drug targets *M. tuberculosis* by inhibiting catalase-peroxidase, an enzyme that neutralizes oxidative stress, and enoyl-acyl-carrier-protein reductase, which is important for producing mycolic acids [89,93]. This combined action compromises the bacterial cell wall and disrupts the metabolism of lipids, carbohydrates, DNA, and nicotinamide-adenine-dinucleotide [93]. Consequently, this bactericidal drug inhibits cell wall synthesis in *M. tuberculosis*, thereby eliminating active metabolizing extracellular bacilli [94]. Due to the potent bactericidal activity of isoniazid during the intensive treatment phase, it complements the other first-line companion TB drugs [94]. Isoniazid interferes with the therapeutic and pharmacological effects of vitamin B6 during neurotransmitter biosynthesis; therefore, vitamin B6 supplementation is imperative to prevent isoniazid-induced peripheral neuropathy [17,95]. Although neurological and hepatic toxicity are uncommon in pediatric patients, the risk increases in those receiving high-dose isoniazid therapy, in HIV-positive patients, and in malnourished individuals [96].

Despite the increasing prevalence of rifampicin-resistant TB strains, *rifampicin* remains a front-line drug in the first-line TB treatment regimen [8,97]. It is a semisynthetic drug that is derived from the rifamycin class, which is part of the ansamycin antibiotic family [92,98]. Rifampicin exerts antimicrobial bactericidal effects by inhibiting DNA-dependent RNA polymerase through binding to its β -subunit and affecting the mRNA synthesis, preventing RNA transcription and consequently interrupting protein synthesis [89,91,92,94,98]. It is worth mentioning that bacterial RNA polymerase binds rifampicin more readily than mammalian RNA polymerase; however, this selectivity does not preclude rifampicin from causing side effects [97]. The most notable side-effect seen is the orange-red discoloration of tears, sweat, and urine, while hepatic adverse effects are uncommon in pediatric patients [99]. Moreover, rifampicin exhibits bactericidal activity against both extracellular and intracellular *M. tuberculosis*, aiding its overall bactericidal activity [94,97]. Nonetheless, there are critical gaps associated with rifampicin treatment, including long-term side effects (typically diarrhea, nausea, vomiting, and anorexia); the risk of developing rifampicin resistance when used as monotherapy or as a result of inadequate rifampicin exposure in fixed-dose combination formulations; and CYP450 family metabolic activity induction [98]. Subsequent sections will explore these limitations associated with rifampicin and its treatment in more detail.

Pyrazinamide is another standard drug in the TB treatment regimen and is a vital component in the current “short course” therapy [100]. It exerts potent bactericidal effects against *M. tuberculosis* bacilli [94,100]. The distinctiveness of pyrazinamide lies in its ability to target semi-dormant bacilli under acidic conditions and to eliminate “persister” bacteria that survive despite unfavorable conditions within the acidic centers of the caseating granulomas [100]. Similar to isoniazid, pyrazinamide is a prodrug that is converted to its active metabolite, pyrazinoic acid, through nicotinamidase, which is the bacterial pyrazinamidase enzyme that subsequently terminates the *M. tuberculosis* bacilli within the granulomas [89,92]. Nevertheless, the exact mechanism of action by which it exerts its effects remains enigmatic [92]. Common side effects include joint discomfort, gastrointestinal distress, and hepatotoxicity. However, while liver toxicity in adults depends on treatment dosage and duration, it is uncommon in pediatric patients, where it usually causes only minor liver enzyme alterations [17]. Moreover, the hepatotoxic effects of pyrazinamide may be exaggerated when used in combination with isoniazid and rifampicin [94].

Ethambutol is a known bacteriostatic agent that acts as a complementary drug within the first-line group of antitubercular drugs [94]. It inhibits mycobacterial cell wall synthesis by interfering with arabinogalactan synthesis through inhibition of the arabinosyl transferases enzyme [91,93,101] and aids in protecting against drug-resistant mutations [85,94]. Ethambutol monotherapy should be avoided, as it not only results in resistance to itself but also leads to isoniazid tolerance if the latter is consequently implemented [94,102]. However, ethambutol exerts a synergistic effect by improving the activity of other companion antitubercular drugs, such as rifampicin and isoniazid [101,103]. It also increases bacterial sensitivity to isoniazid [101]. Another important reason for incorporating

ethambutol is its role in preventing rifampicin resistance, especially in instances where isoniazid monoresistance might be present [104].

Historically, the use of ethambutol in children younger than five years was not recommended and was often considered contraindicated due to a common side-effect associated with this drug, namely optic neuritis [85,105]. Diagnosing this condition in this particular age group is challenging due to their inability to verbalize and comprehend symptoms; however, although delayed diagnosis can result in irreversible blindness, early detection followed by prompt discontinuation of this drug can reverse this adverse effect [85]. Fortunately, when proper dosing guidelines are adhered to, the risk of toxicity in pediatric populations is negligible, as this side effect is both dose- and duration-dependent [85]. Ultimately, its use is determined by careful risk-benefit ratio assessment.

4. Rifampicin: Characteristics and Challenges

4.1. Physicochemical Properties and Rifampicin Instabilities

Rifampicin, presented in Figure 2, is a semi-synthetic derivative of rifamycin B, characterized by the rifamycin *ansa* structure, which consists of a condensed furan and naphthalene core linked by a substituted aliphatic chain bridging two nonadjacent sites of the naphthoquinone ring [106,107]. Interestingly, this chromophore is responsible for the characteristic color of rifampicin [106,108]. This macrocyclic antibiotic presents as an odorless crystalline powder with a brownish-red to reddish-brown color [107,109,110]. Rifampicin ($C_{43}H_{58}N_4O_{12}$, 822,95 g/mol) has a melting point of 183–188°C [39,111].

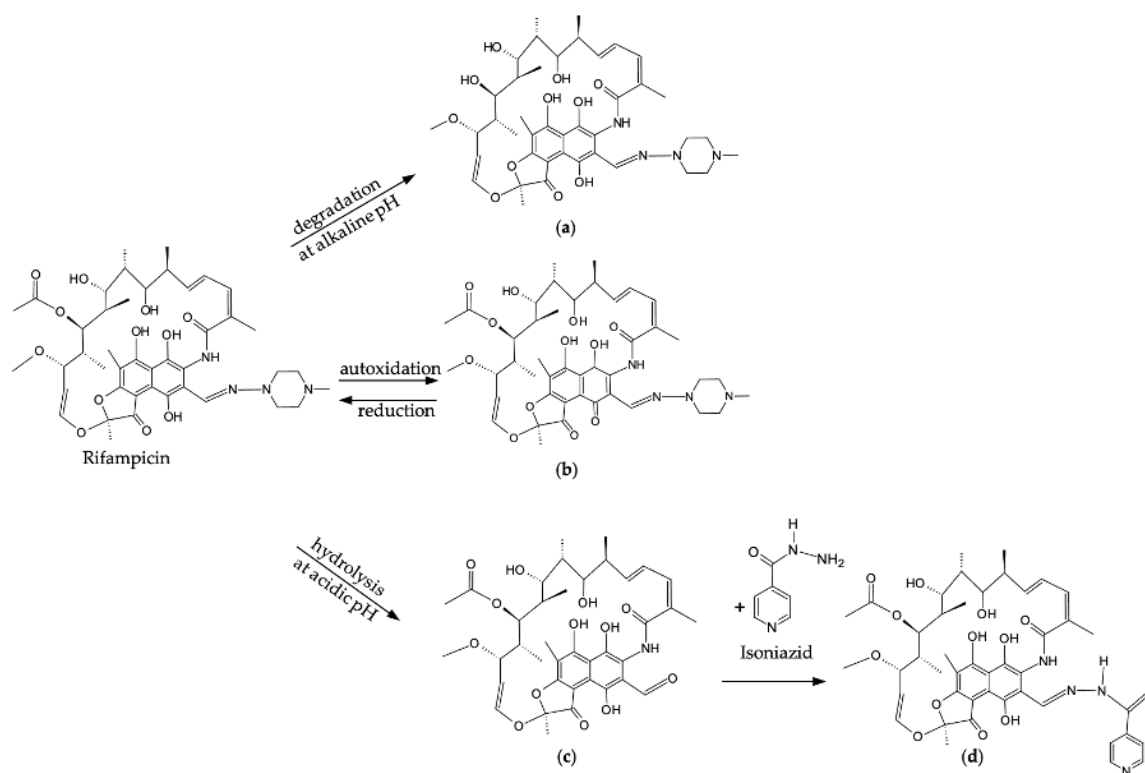


Figure 2. Degradation pathways of rifampicin: (a) 24-diacetyl rifampicin; (b) rifampicin quinone; (c) 3-formyl rifamycin SV; (d) 3-formyl-rifamycin-isonicotinylhydrazone. Adapted from [112].

Rifampicin exerts conformational polymorphism, with Polymorphs I and II varying in both bioavailability and physicochemical properties [107,113,114]. Polymorphic Form I is considered the most stable form of rifampicin, and Form II is the metastable crystalline polymorphic form [107]. Characterization of some commercial rifampicin bulk samples indicated the presence of Form I, Form II, and amorphous states; however, these polymorphic variations confer minimal solubility

advantage, rendering these differences both regulatory and clinically insignificant [114]. From a chemical perspective, rifampicin is a hydroquinone derivative containing three phenolic –OH groups that are prone to electrochemical or chemical oxidation [106]. Rifampicin possesses both an acidic *p*-hydroxy naphthyl ketone and a basic piperazine amine, with pK_a values of 1.7 and 7.9, respectively. These confer amphoteric properties, enabling rifampicin to adopt a zwitterionic form depending on the pH of the medium in which it is presented [32,106,107,115].

Rifampicin is a lipophilic drug, with a log P value of 3.85, enabling it to partition into the hydrophobic cell wall of *M. tuberculosis* and potentially also the caseum [116]. Consequently, exploiting these properties can enhance the therapeutic efficacy of rifampicin in TB treatment [116]. Furthermore, the physicochemical properties of rifampicin contribute to its limitations as an ideal therapeutic agent. For instance, rifampicin exhibits pH-dependent solubility, which is further influenced by solvent types [109,117]. Although rifampicin demonstrates maximum chemical stability at pH 6 [118,119], its solubility increases in acidic environments such as the gastric milieu (pH of 1–3), with a maximum solubility at pH 1–2 [39,41]. This hydrophobic drug [110] is poorly soluble in acetone and in water (pH<6), with an aqueous solubility of 0.10 ± 0.01 mg/mL; it is soluble in methanol and ethyl acetate, and freely soluble in methyl chloride, dimethyl sulfoxide, and chloroform [106,109,117]. Alves *et al.* reported a significant decrease in rifampicin solubility from 100 mg/mL at pH 2 to 4 mg/mL at pH 5.3, with a further reduction to 2.8 mg/mL at pH 7.5 [120].

Rifampicin absorption predominantly occurs in the duodenum (pH 4–6), despite its relatively lower solubility in this region [120]. According to the Biopharmaceutical Classification System (BCS), rifampicin, previously categorized as a Class II drug, has recently been reclassified as a Class IV drug due to its limited intestinal permeability and poor aqueous solubility [121].

Rifampicin is available in both intravenous and oral formulations; however, the oral route is typically preferred, since intravenous administration is reserved for severe infections and is often associated with immunological reactions and adverse effects, which in turn can compromise patient compliance [110,122,123]. Limited research indicates significant differences in drug disposition between adults and pediatric populations, especially in infants [124–128]. This variation can likely be attributed to Cytochrome P450 (CYP) ontogeny, which begins shortly after birth and matures to adult levels between the ages of 1–10 years [122,124]. Rifampicin is, furthermore, a potent inducer for various enzymes, including permeability-glycoprotein (P-glycoprotein), 5'-diphosphoglucuronosyltransferase (UGTs), and CYP P450 isoenzymes, where CYP3A4 specifically mediates the autoinduction of rifampicin [129,130]. This drug undergoes hepatic deacetylation primarily through CYP3A4 to form its main metabolite, 25-diacetyl rifampicin, with the involvement of CYP2C isoenzymes such as CYP2C8, CYP2C9, CYP2C18, and CYP2C19 [123,125,129]. Figure 2 (a) illustrates the degradation pathway of rifampicin to form 25-diacetyl rifampicin under alkaline conditions [112]. Furthermore, since rifampicin is a potent CYP3A4 inducer, drug-drug interactions merit consideration, as they can result in suboptimal drug levels [122,129]. Therefore, the enzymatic instability of rifampicin further challenges its therapeutic efficacy [112,122,129].

Moreover, numerous challenges, such as efflux pump-mediated extrusion, resistance development, first-pass hepatic metabolism, limited intracellular bacterial accumulation, and peripheral neuropathy are associated with this gold-standard antitubercular drug [110]. The clinical efficacy of this drug is also compromised by adverse dose-dependent effects and inadequate drug penetration as a result of poor vascularization of pathological loci [110]. Rifampicin is subjected to enterohepatic circulation and is predominantly eliminated by means of the urinary and biliary routes [106,123,125]. In pediatrics, aged 3 months to 12 years, the half-life of rifampicin is approximately 2 hours [122].

A persistent challenge that continues to undermine TB treatment is the pronounced chemical instability of rifampicin [106,115,131,132], which is influenced by various factors such as the storage temperature and duration, light exposure, ionic strength of the solution, solvent type, and the pH of the medium [106,118]. In addition, rifampicin exhibits a high propensity for drug-drug interactions, which further compromises its bioavailability [30,32,38,123]. The degradation rate of rifampicin,

being an endothermic reaction, accelerates significantly with an increase in storage temperature and prolonged duration, especially above 40°C [118]. Moreover, the degradation of this light-sensitive drug [132] is also accelerated by increased ionic strength in solution [118].

Rifampicin quinone, the primary degradation product of rifampicin, is formed through nonenzymatic autoxidation when in solution [131] – a temperature-dependent reaction that is potentiated under alkaline conditions, Figure 2 (b) [112,131,133]. Oxidation of rifampicin occurs in two steps: first, the hydroquinone functional group reversibly oxidizes to benzoquinone; second, the phenolic ring of rifampicin undergoes irreversible oxidation [133]. Rifampicin quinone is considered an impurity, as its presence in pharmaceutical formulations serves as an indicator of poor quality [109,131,132]. Interestingly, while rifampicin quinone exerts a limited antimicrobial effect, it retains distinct anti-inflammatory and immunosuppressive properties [134]. Under physiologically relevant temperatures and in solution, rifampicin quinone can undergo temperature-dependent chemical conversion to form rifampicin; nonetheless, its presence limits the bioavailability of rifampicin and contributes to the development of antimicrobial resistance [32,131–133]. Weinstein and Zaman [135] demonstrated that resistance to rifampicin quinone alarmingly confers cross-resistance to relevant clinical rifamycins, for example, rifampicin, rifapentine, and rifabutin. It is also evident that rifampicin quinone promotes rifampicin resistance in *M. smegmatis* and *Escherichia coli* [135]. It is worth mentioning that the other first-line anti-TB drugs can react with rifampicin quinone via their free amino groups; the reaction rate is high in alkaline environments and low in acidic environments, with ethambutol and pyrazinamide exhibiting the highest and lowest reaction rates, respectively [133].

The formulation of an acceptable drug delivery system for rifampicin is further complicated by its susceptibility to degradation, especially under acidic conditions [32,39,115]. Under such conditions, the azo-methine group of rifampicin undergoes reversible acid hydrolysis, resulting in the formation of 1-amino-4-methylpiperazine and 3-formyl-rifamycin SV, Figure 2 (c) [30,39,120]. The bioavailability of rifampicin is further reduced with the formation of 3-formyl-rifamycin SV, a poorly soluble compound that exerts *in vitro* antimicrobial activity but remains inactive *in vivo* [30,112,132]. It is worth noting that *in vivo* degradation is enhanced in fasting subjects with gastric pH values of 1.4–2.1 [12,38,112].

Furthermore, under acidic conditions, 3-formyl-rifamycin SV forms can subsequently react with isoniazid via a second-order reaction to form hydrazone, which, if unstable, can revert to 3-formyl-rifamycin SV and isoniazid through a pseudo-first-order reaction, Figure 2 (d) [12,38,112,136]. Since the second-order reaction occurs more rapidly than both the initial rifampicin and 3-formyl rifampicin reaction and the hydrazone with 3-formyl-rifamycin SV and isoniazid first-order reaction, the overall predominant response is hydrazone formation [12,132]. As shown in Figure 3, hydrazone is formed via a direct reaction between rifampicin and isoniazid, where the amino group of isoniazid nucleophilically attacks the imine group of rifampicin through a tetrahedral mechanism [38]. Consequently, this insoluble metabolite further exacerbates the poor bioavailability of rifampicin [12,30,32,38,132].

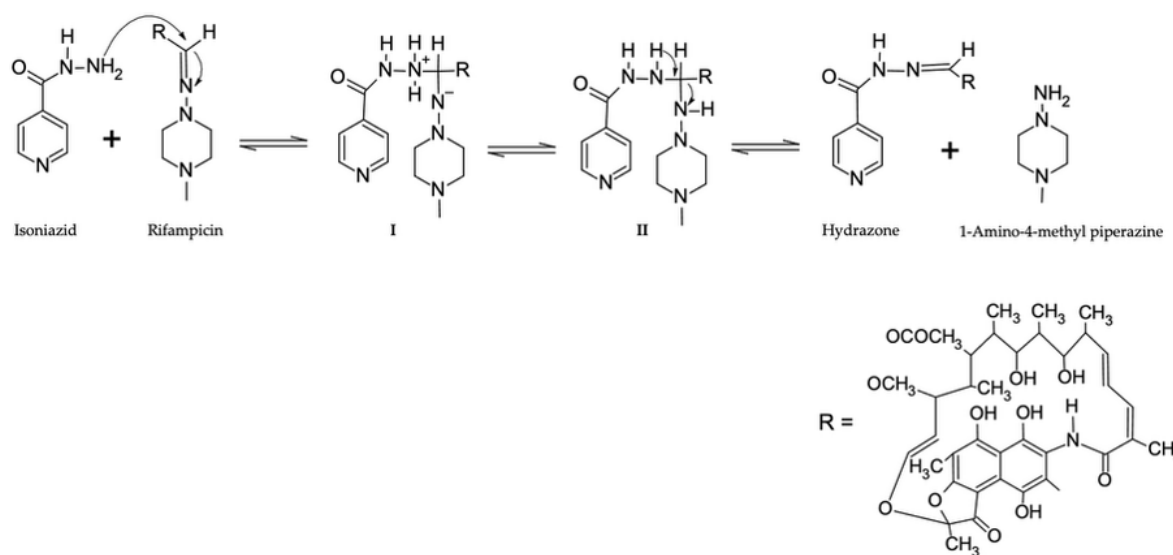


Figure 3. The interaction between rifampicin and isoniazid (also known as isonicotinylhydrazide) results in the formation of hydrazone. (I) first intermediate; (II) second intermediate. Adapted from [30,38].

Considering the above, it was concluded that rifampicin and isoniazid decomposition in a fixed-dose combination with pyrazinamide could not be attributed solely to the direct transhydrazone formation between rifampicin and isoniazid. Instead, pyrazinamide plays a catalytic role in the decomposition process [38]. Therefore, the presence of pyrazinamide accelerates the decomposition via a base-catalyzed transhydrazone formation, mainly resulting in hydrazone. Pyrazinamide and ethambutol catalyze the decomposition of rifampicin and isoniazid through different mechanisms [38]. Ethambutol (both as the hydrochloride salt and free base), on the other hand, exerts a stronger catalytic effect than pyrazinamide due to its ethylenediamine or 1,2-amino alcohol functional group, which can abstract protons from two isoniazid molecules simultaneously. This results not only in hydrazone formation but also in additional degradation products, such as rifampicin-N-oxide and 25-desacetyl rifampicin, especially under alkaline conditions [38].

Therefore, it is not surprising that fixed-dose combination products comprising rifampicin, isoniazid, pyrazinamide, and/or ethambutol exhibit significantly greater chemical instability compared to rifampicin and isoniazid fixed-dose combinations [38]. Various strategies have been employed to prevent the undesirable interaction between rifampicin and isoniazid, to enhance the stability and, consequently, the bioavailability of rifampicin [137–141]. Although some studies have reported improved outcomes, the variable and poor bioavailability of rifampicin, most pronounced in fixed-dose combination formulations, remains a topic of considerable concern. Hence, the development of a stable, independent rifampicin formulation should be prioritized to ensure consistent bioavailability before it is incorporated into fixed-dose combination products.

4.2. Available Child-Friendly Rifampicin Dosage Forms

Despite the pivotal role of rifampicin in TB management since the 1960s and the alarming statistics of active pediatric TB cases, the majority of TB medicines remain adult-focused; a disquieting reality that underscores the persistent and widespread neglect of pediatric TB [8,12,46,85,98]. This is evident by the prevailing assumption that children are merely ‘small adults’, as pediatric TB treatment regimens are typically extrapolated from those of adults, necessitating adjustments for weight and age [17,43,44,46,48,142]. Such extrapolations can compromise pediatric treatment safety and efficacy, as extemporaneous preparations or the manipulation of adult formulations often result in suboptimal dosage forms with inaccurate weight-based dosing [12,37,45,46,85,142].

According to research, most commercially available drug products prescribed for pediatric TB are not available as child-friendly dosage forms, which contributes to poor adherence and, in turn,

exacerbates morbidity and mortality from drug-resistant TB in children [17,45,46,48,49,143]. Notwithstanding these concerns, the development of child-friendly TB dosage forms remains limited. Pharmaceutical companies and research are deterred by this high-risk, small, and less lucrative population, which continues to impede the development of child-friendly medicines [12,17,37,45,144]. It is important to realize that, even when pediatric TB formulations exist, their clinical availability varies considerably across the world [48].

First-line TB drugs are available in water-dispersible fixed-dose combination formulations through the Stop TB Global Drug Facility, enabling more precise dosing and circumventing the need for extemporaneous preparations of adult dosage forms [143,145]. Besides the absence of child-friendly rifampicin-only formulations [145], these water-dispersible fixed-dose combination formulations are not widely available worldwide, especially in countries with low TB rates. [69,144,146].

Furthermore, a study by Wademan *et al.* revealed that, even with clear instructions on the proper administration of water-dispersible fixed-dose combination tablets, caregivers often modified the medicine using various strategies to improve pediatric TB treatment administration [37]. These strategies included administering the water-dispersible fixed-dose combination formulations in their solid tablet form or mixing them with fluids or food (for example, porridge, yoghurt, or water) to improve their poor palatability [37,45,53]. Such approaches are often employed in resource-constrained countries due to restricted access to safe water [48,144]. However, further research is required to determine the pharmacokinetic impact of these real-world administration practices [37,45]. Pragmatic challenges, including the time-intensive administration process and the need to dissolve the dispersible tablet, also hinder caregivers from integrating this treatment within their daily routines [37]. Furthermore, inadequate reconstitution of dispersible formulations can cause tissue injury (similar to tablets adhering to the esophagus) and prolong drug onset of action [142].

The WHO recommends the administration of fixed-dose combination formulations that combine drugs for both the intensive and continuation phases of TB treatment [86]. However, the available pediatric fixed-dose combinations for the intensive phase contain rifampicin and isoniazid in a 2:1 ratio instead of the recommended pediatric ratio of 1.5:1. As a result, additional isoniazid tablets are often required to achieve recommended weight-based dosing [48,85,147]. Moreover, the currently available child-friendly dispersible fixed-dose combination fails to provide adequate doses, underscoring an urgent need for higher dose formulations [146]. Pediatric patients often require higher dosages of rifampicin to attain serum concentrations extrapolatable to those in adults [85,147]. Additionally, higher rifampicin doses may be critical in severe TB forms, such as miliary TB and TB meningitis [146].

Aside from the advancements in the development of child-friendly dosage forms for drug-susceptible TB, the persistent absence of a rifampicin-only formulation [146] delineates a critical and unmet therapeutic need. Although rifampicin oral suspension is theoretically available globally, its absence in real-world practice is striking [143]. Alarming, in South Africa – where the TB burden is among the highest – the only available liquid rifampicin formulation has been withdrawn [50]. Furthermore, previous rifampicin oral suspensions failed to achieve target drug concentrations in the pediatric population at the recommended doses, plausibly attributed to its poor bioavailability [148].

4.3. General Requirements and Considerations for Child-Friendly Dosage Forms

Acceptability can be described as “the overall ability and willingness of the patient to use, and of the caregiver to administer, the medicine as intended” [53]. This paramount requirement ensures optimal adherence to treatment, hence, safeguarding both the safety and efficacy of TB therapy [53]. Enhancing pediatric acceptability, and consequently, adherence to rifampicin treatment, necessitates consideration of characteristics that are both age-appropriate and acceptable across this heterogeneous population [149].

However, non-adherence to pediatric medicines is particularly arduous to circumvent due to multifactorial influences such as socioeconomic status, cultural background, health literacy, family

structure, and age [142,143,150]. This represents a multifaceted problem encompassing the collective involvement of interdisciplinary healthcare teams, caregivers, and the patient [150]. Despite the growing availability of child-friendly dosage forms, including dispersible and mini-tablets, oral liquid formulations remain the preferred choice for children under 12 years and their caregivers, owing to their palatability, flexible dosing, ease of administration, and suitability across the pediatric population (including infants) [12,37,142,144,149]. Furthermore, the swallowability of liquid formulations reduces the risk of choking and benefits not only the pediatric population but also the general population, particularly those with swallowing difficulties [12,149].

Pediatric acceptability towards treatment is strongly influenced by key attributes, prioritized as follows: taste, swallowability, ease of administration, mouthfeel/texture, color/appearance, smell, and aftertaste. Notably, pediatric patients are more sensitive to sensory characteristics than adults [37,53,144,149]. Therefore, formulation-related factors, particularly the recalcitrance and organoleptic characteristics of the dosage form, constitute significant contributors to treatment non-adherence in this population [150]. The unpalatability of first-line anti-TB drugs is often cited as the main cause of treatment non-adherence in children. Rifampicin, in particular, is considered the most bitter [37,151]. What further exacerbates the complexity of this problem is the pronounced sensitivity of the pediatric population to excipients intended to enhance palatability, coupled with the frequent exclusion of pediatric patients from clinical trials, rendering the ethical development of child-friendly dosage forms particularly challenging [17,53]. Although the 2013 *Guideline on Pharmaceutical Development of Medicines for Pediatric Use* (EMA/CHMP/QWP/805880/2012 Rev. 2) issued by the European Medicines Agency emphasized the importance of incorporating pediatric medicine acceptability into clinical studies, achieving adequate pediatric medicine acceptability in practice remains a persistent barrier to safe and efficient treatment [53]. To this day, an urgent need remains to develop appropriate, palatable, child-friendly rifampicin formulations to ensure optimal pediatric TB treatment outcomes [12,17].

5. Can the Therapeutic Efficacy of Rifampicin Liquid Formulations be Improved?

Approximately 70% of currently available drug candidates belong to BCS class II (i.e., low solubility and high permeability), while an additional 20% fall under BCS class IV (low solubility and low permeability) [152,153], rendering most anti-TB drugs sparingly soluble in aqueous media. Nevertheless, to address these persistent formulation challenges associated with poorly soluble drugs, lipid-based formulations have become a leading strategy [154–157]. The potential of these drug delivery systems to improve the delivery of various anti-TB drugs has been extensively investigated, owing to their favorable biopharmaceutical attributes [29,39,158].

Typically composed of fatty acid esters, lipid-based drug delivery systems constitute a continuum from simple drug-in-oil formulations to advanced delivery systems capable of spontaneously emulsifying in an aqueous environment [159,160]. These novel lipid-based formulations – including emulsions, lipid particulate systems, and vesicular systems, along with their subcategories – offer commercially viable options for developing effective and safe pharmaceuticals for ocular, oral, pulmonary, parenteral, and topical delivery routes of administration [159,161].

Self-emulsifying drug delivery systems (SEDDSs), a subset of these formulations that rely on spontaneous emulsification, have attained broad recognition as a well-established approach for the oral administration of poorly soluble drugs [156,162,163]. The development of rifampicin lipid-based delivery systems, particularly SEDDSs, presents a promising approach to overcome several of the aforementioned challenges [163].

5.1. Self-Emulsifying Drug Delivery Systems

SEDDSs are emulsion concentrates comprising a drug incorporated into a mixture of oil, surfactants, and, in some cases, co-surfactants and/or co-solvents [152,159,163]. In their initial state,

SEDDSs are not emulsions; however, upon mild agitation in the aqueous environment of the stomach, spontaneous emulsions are formed [152,161,163,164]. Consequently, these delivery systems provide an effective means of improving the solubilization of poorly aqueous soluble drugs [152,163]. The presence of these minute oil-in-water droplets within the gastrointestinal tract bypasses the dissolution stage typically required for dispersed powders, thereby facilitating improved drug solubilization and absorption [162]. Unlike other lipid-based formulations, SEDDSs demonstrate a promising approach for achieving higher drug-loading capacities [157]. This improvement can be ascribed to the enhanced solubility of poorly water-soluble drugs, particularly those with an intermediate partition coefficient ($2 < \log P < 4$), within the formulation's co-surfactant and amphiphilic surfactant components [157].

SEDDSs production involves a comparatively straightforward and less intricate formulation process than that of conventional emulsions. This process entails mixing oil, surfactants, and/or co-surfactants, followed by the addition of the drug and vortexing to obtain a clear, homogeneous solution. Alternatively, the drug may first be dissolved in one or more excipients before combining with the remaining components. This approach enables the construction of a pseudoternary phase diagram for the identification of the optimal self-emulsification region. Moreover, the methodologies governing SEDDS development are well-established and comprehensively documented in scientific literature [39,165,166].

The term *SEDDS*, however, is a broad term encompassing several specific lipid-based drug delivery systems, which are primarily distinguished into three categories according to droplet size. Based on their preparation method and composition, drug-loaded SEDDSs can be formulated as conventional SEDDSs, self-microemulsifying drug delivery systems (SMEDDSs), or self-nanoemulsifying drug delivery systems (SNEDDSs) [155,163,165]. The general properties and composition of these systems are briefly summarized in Table 2; however, these properties represent overall trends and may vary depending on specific formulation parameters. Additionally, lipid-based formulations are categorized within the Lipid-Based Formulation Classification System (LFCS) according to their composition and behavior upon dispersion within an aqueous environment [152,155,167]. LFCS divides lipid-based formulations into four types (I–IV), with conventional SEDDSs, SMEDDSs, and SNEDDSs as type II, type IIIA/IIIB, and type IIIB, respectively [162,167,168].

Table 2. Comparative properties of SEDDSs, SMEDDSs, and SNEDDSs [161,162,165,167].

Property	SEDDSs	SMEDDSs	SNEDDSs
Average droplet size	>300 nm	100–200 nm	<100 nm
Appearance	Cloudy/turbid	Clear to translucent	Optically clear
Bioavailability	Moderate	Enhanced	Superior
Classification as per LFCS	Type II	Type IIIA/IIIB	Type IIIB
Concentration of oil	40–80%	40–80%/<20%	<20%
Concentration of surfactant	30–40%	40–80%	40–80%
HBL of surfactants	<10	10–12	>12
Oil types	Long-chain triglycerides	Medium-chain triglycerides	Medium- and short-chain triglycerides
Solubilizing capacity	High	High	High
Stability	Thermodynamically unstable	Thermodynamically stable	Kinetically stable

The successful formulation of a SEDDS of maximal therapeutic efficacy necessitates consideration of several key factors, including the physicochemical properties of both the drug and the excipients, drug-excipient interactions (*in vivo* and *in vitro*), and the physiological factors that may impede or enhance bioavailability [156]. Furthermore, formulation design must also account for

practical considerations such as the cost of materials, regulatory status, miscibility, solubilization capacity, the physical state of excipients at ambient temperature, and chemical stability [156,159,163]. This systematic and rational approach serves to both expedite the formulation development process and reduce the associated costs [156].

5.1.1. Composition of Self-Emulsifying Drug Delivery Systems

Drugs. As per the BCS, Class II and IV drugs, characterized by poor solubility, are often prime candidates for lipid-based delivery, as these systems can significantly enhance solubility and absorption. However, formulation efficiency is strongly influenced by physicochemical properties such as solubility, partition coefficient, molecular weight, and chemical stability within the gastrointestinal tract [156,162]. Ideally, a drug should possess a log P value of at least 2 [157]. In general, drugs with a log P value greater than 5 exhibit optimal solubility in the oil/lipid, surfactant, and co-surfactant/co-solvent phases, thereby promoting efficient absorption through intestinal epithelial cells and subsequent integration into chylomicrons [157]. Moreover, these highly lipophilic drugs possess enhanced solubility in lipid phases and improved absorption through lymphatic transport, effectively bypassing hepatic first-pass metabolism. Nevertheless, such drugs may also encounter formulation challenges, including precipitation upon dilution [156].

Oils/lipids. Within SEDDSs, the oil phase solubilizes the lipophilic/hydrophobic drug, thereby increasing both drug-loading capacity and oral bioavailability [156]. The hydrophilic-lipophilic balance (HLB), physical properties, and melting characteristics of glycerides depend on the nature of the fatty acid composition, degree of esterification, and their interaction with glycerol to produce mono- or diglycerides [166]. Lipids are commonly classified according to fatty acid chain length into short-chain triglycerides (<5C), medium-chain triglycerides (C6–C12), and long-chain triglycerides (C14–C20) [152,156,161,163,166].

Medium-chain triglycerides, such as coconut-derived glyceryl tricaprilate, are widely used in SEDDSs due to their high oxidative stability and superior solvent capacity [152,156,161,163,166]. Long-chain triglycerides, predominantly found in fixed oils such as vegetable oils, consist mainly of glyceride esters derived from unsaturated long-chain fatty acids. These are generally regarded as safe and readily digestible [156,161]. The substantial hydrophobic domains of both medium- and long-chain triglycerides confer considerable solubilization potential for lipophilic drugs. Upon digestion, short- and medium-chain triglycerides are absorbed through the portal vein, whereas long-chain derived chylomicrons promote lymphatic transport [156,160,168]. The self-emulsification process enhances solubility by reducing interfacial tension between the water and oil interface, and modulating the time and curvature of the interfacial film, by minimizing precipitation [166].

A study by van Deventer et al. [39] demonstrated that although rifampicin exhibited higher solubility in olive oil (0.46 ± 0.12 mg/mL) than in water, its solubility in the olive oil remained lower than what was anticipated. Olive oil is predominantly composed of fatty acid components such as palmitic acid (11–12%), oleic acid (about 76–77%), as well as smaller quantities of linoleic, linolenic, palmitoleic, and stearic acids. These components contribute to lowering the pH of the oil to approximately 5.17 at ambient temperature, which further decreases to about 4.49 during storage as the %oleic acid (free oil acidity) increases. As a result, these factors limited rifampicin solubilization and promoted its degradation over 24 hours, emphasizing the importance of selecting an appropriate oil phase in SEDDSs containing rifampicin [39].

Surfactants. Amphiphilic molecules, or surfactants, contain both lipophilic and hydrophilic functional groups, enabling them to reduce interfacial tension at the oil-water interface [156,161]. They are classified as ampholytic, anionic, cationic, or non-ionic, depending on their ionization behavior in aqueous media [161]. In SEDDSs, the drug-loaded oil phase is dispersed into minute droplets, significantly increasing the surface area and, therefore, requiring adequate surfactant concentrations to ensure solubilization [169].

Excessive surfactant concentrations, however, can paradoxically increase droplet size by promoting water infiltration into the oil droplets and disrupting the interfacial film. High surfactant

concentrations may also cause gastrointestinal irritation [156]. The required surfactant concentration varies with the oil's molecular volume, with long-chain triglycerides typically necessitating higher surfactant levels than short-chain di- or monoglycerides. The hydrophilic-lipophilic balance (HBL) determines the emulsion type formed, i.e., oil-in-water, water-in-oil, or bicontinuous emulsions [156].

Nonionic surfactants are predominantly preferred in SEDDSs due to their reduced critical micelle concentrations, low toxicity, and high stability across a wide pH range. Moreover, they do not interact with ionic drugs and are effective in reducing interfacial tension at relatively low concentrations [152,166,169]. Certain surfactants and lipids can also inhibit intestinal efflux transporters such as P-glycoprotein and metabolic enzymes (i.e., CYPs), enhancing drug absorption [168]. Additionally, combinations of oils and/or surfactants, along with their digestion products, can increase intestinal permeability by fluidizing cell membranes and opening tight junctions [168]. Collectively, these properties render surfactants indispensable for the stabilization of fine droplets, improved solubilization, and enhanced bioavailability of lipophilic drugs.

Co-surfactants/co-solvents. Co-surfactants further reduce transient negative interfacial tension, and in turn, they impart interfacial film flexibility, enabling varied curvatures necessary for achieving diverse microemulsion concentrations [170]. Moreover, the addition of co-surfactants simulates higher surfactant amounts, [170], thereby facilitating the formation of finely dispersed droplets. While the film becomes adequately depleted, the positive interfacial tension is restored through the absorption of additional surfactant or adjustment of the surfactant-to-co-surfactant ratio, leading to spontaneous emulsification [171].

Co-solvents, on the other hand, improve the solubilization of incorporated drugs and aid in the dispersion of hydrophilic surfactants within the oil phase, which helps maintain stability and uniformity [168]. Accordingly, co-surfactants and co-solvents act synergistically with surfactants to enhance emulsification, minimize drug precipitation, and augment thermodynamic stability, ensuring uniform drug delivery and optimal absorption [162].

5.2. Optimizing Pediatric Oral Bioavailability of Lipophilic Drugs

The inclusion of poorly aqueous soluble or lipophilic drugs, for example, rifampicin, within a formulation remains an arduous endeavor, since their solubility and absorption in the aqueous environment of the gastrointestinal tract are inherently limited [154,160]. The observed enhancement in the bioavailability of lipophilic drugs when co-administered with fat-rich meals has prompted significant interest in developing oral lipid-based formulations designed to increase drug solubilization in the gastrointestinal tract [164,172]. Poor oral bioavailability may result from multiple interrelated factors, of which adequate solubility within the gastrointestinal lumen is a critical prerequisite, particularly in pediatric patients [154,168]. To fully elucidate the mechanisms and benefits of lipid-based formulations, it is fundamental to grasp the physiological response of the body to lipid intake, while considering the distinct subgroups within the pediatric population [154,155].

After oral administration, the presence of lipid-enriched chyme in the duodenum elicits the secretion of the intestinal peptide hormone cholecystokinin. Cholecystokinin induces simultaneous relaxation of the hepatopancreatic sphincter and contraction of the gallbladder, leading to the release of bile – comprising bile salts, cholesterol, and phospholipids (predominantly phosphatidylcholine) – into the small intestine [172,173]. Concurrently, pancreatic fluids containing lipase and co-lipase are released into the intestines [173]. In addition, pancreatic phospholipase A hydrolyzes endogenous and biliary- or formulation-derived phospholipids to produce free fatty acids and lysophosphatidylcholine, which together contribute to the formation of mixed micelles [173].

The digestion and absorption of endogenous lipids provide an interactive and dynamic conduit for rifampicin delivery and other lipophilic drugs [172]. During lipid digestion, pancreatic lipases convert triglycerides into fatty acids, monoglycerides, and diglycerides [163,172]. These enzymatic processes naturally promote the solubilization of ingested lipids, while gastric lipolysis, albeit to a lesser extent, initiates lipid emulsification. Lipid digestion continues in the small intestine via pancreatic esterases and lipases, during which bile constituents combine with phospholipids to form

bile-phospholipid mixed micelles that result in various colloidal structures [160,165,173]. These highly dispersed small colloidal entities aid in the solubilization of ingested poorly water-soluble lipids [173] and facilitate the transport of hydrophobic molecules across the viscous unstirred water layer to the absorptive surface of the intestinal epithelium [172].

Because rifampicin exhibits restricted transport across the viscous unstirred water layer [169], it is particularly well-suited to absorption enhancement through lipid-based formulation strategies. Although the concept of lipid-based formulations was initially inspired by the co-administration of lipophilic drugs together with a fat-rich meal, co-administration thereof, especially in the case of rifampicin, can alter drug-lipoprotein interactions and lymphatic transport, potentially enhancing drug plasma concentrations [163,172].

Lipid-based formulations are designed to exploit these intrinsic lipid digestion pathways, thereby creating an ideal microenvironment in which lipophilic drugs with pronounced lipid affinity can partition into exogenous lipid carriers [165,173]. The digested lipid products, along with the solubilized drug, are absorbed upon reaching the enterocytes of the gastrointestinal wall [160,165]. Bile-phospholipid mixed micelles mediate the physiological effect of exogenous lipid absorption, serving a dual function: they enhance the solubilization of poorly water-soluble drugs and establish a lipid absorption concentration gradient [165]. Incorporating rifampicin into lipid-based formulations will therefore probably improve gastrointestinal absorption through the formation of solubilized colloidal structures. These solubilized colloids will promote enterocyte-based transport, modulate efflux and uptake mechanisms, and facilitate absorption into the intestinal lymphatic system and systemic circulation [165,174]. Studies have indicated that lipid quantities of merely 2 g are adequate to elicit biliary secretion and augment gastrointestinal bile salt concentrations, which in turn improve intraluminal lipid metabolism and solubilization of drugs [175]. Once a lipophilic drug is solubilized, several mechanisms contribute to lipid-mediated drug absorption after oral administration (Figure 4). These include: (a) facilitated transcellular drug absorption via increased membrane fluidity; (b) surfactant-mediated inhibition of CYP P450 enzymes and/or P-glycoprotein, resulting in an increased intracellular drug concentration and extended residence time; (c) paracellular drug transport through the opening of tight junctions; and (d) lipid-induced lipoprotein and chylomicron production, enhancing lymphatic drug uptake [163].

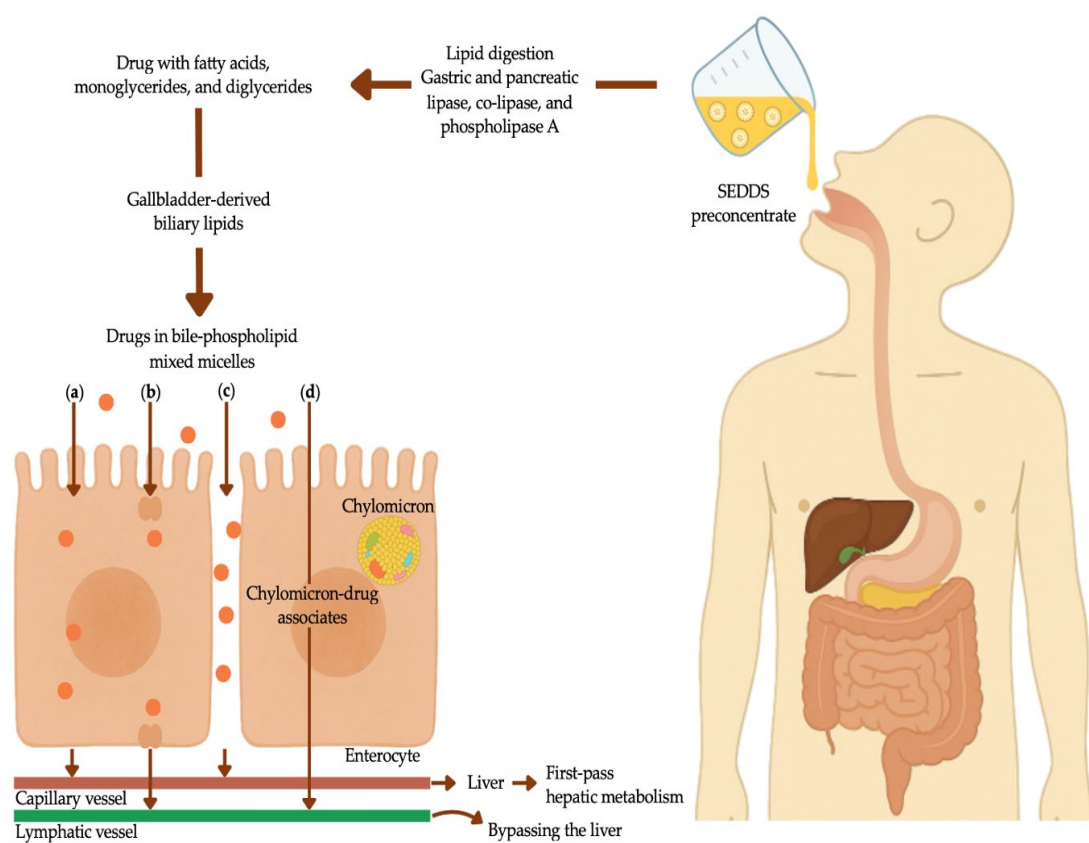


Figure 4. Mechanism by which lipid-based formulations such as SEDSSs facilitate intestinal drug transport.

The intestinal lymphatic system provides an alternative pathway for the transportation of highly lipophilic drugs into the systemic circulation [169]. Long-chain triglycerides with solubility exceeding 50 mg/kg and drugs with a log P value greater than 5, demonstrate limited diffusion across blood capillaries and are therefore preferentially absorbed via the lymphatic pathway [169,176]. Within the enterocytes, chylomicrons act as carriers for these drugs, forming drug-chylomicron complexes that are subsequently transported through the mesenteric lymphatic system to the systemic circulation at the junction of the left subclavian and left jugular veins [169]. This pathway not only bypasses first-pass hepatic metabolism, improving oral bioavailability, but also contributes to site-specific targeting of lymph-manifested diseases such as lymph node TB [163,169,177].

Ontogenetic physiological differences in the pediatric population profoundly affect the solubilization and absorption of lipid-based formulations. Unlike adults, young children exhibit reduced lipase activity, lower bile salt secretion, smaller gastric volumes, and distinct gastric mortality patterns [150,154]. For instance, the immature bile and pancreatic secretions may negatively affect the overall bioavailability of lipid drugs [150]. In neonates, insufficient luminal bile salt concentrations may further impair lipophilic drug absorption, necessitating careful dose adjustments. However, bile salt secretion progressively increases with postnatal maturation, gradually improving lipid drug absorption [150,154]. In infants aged six to eight months, the gastric emptying rate is slower due to immature neuroregulation of gastric motility [150]. Importantly, significant knowledge gaps persist regarding gastrointestinal drug disposition in neonates and infants younger than six months [154].

6. Liquid Self-Emulsifying Drug Delivery Systems as a Novel Approach to Enhance Oral Rifampicin Delivery

Rifampicin, a pillar of anti-TB drug therapy, remains constrained by its physicochemical instabilities and drug interactions. These limitations have long hindered the development of reliable

liquid formulations and perpetuated pediatric TB treatment gaps, particularly in LMICs, where the TB burden is greatest [8,12,38,39,112,123,131,132,136,148].

Various formulation technologies exist to improve drug solubility and mitigate bioavailability issues. Among these, lipid-based formulations such as SEDDSs offer an economically viable solution and are firmly embedded in oral dosage forms [165]. The relevance of SEDDSs in TB treatment stems from their potential to enhance lipophilic TB drug treatment efficacy through improving the solubility and, consequently, bioavailability while also enabling controlled drug release [29,39,158].

Furthermore, it has been demonstrated that effective solubilization of lipophilic drugs can be achieved with lipid quantities as low as 2 g, thereby enabling SEDDSs to facilitate optimal gastrointestinal absorption regardless of low dietary fat intake, an important consideration in TB management [175]. SEDDSs not only improve the stability of highly lipophilic drug emulsions but also support low-cost, scalable manufacturing, offering particular value in LMIC settings. Moreover, these drug delivery systems can protect drugs such as rifampicin from hydrolysis [156,166,172].

In addition, SEDDSs may inhibit P-glycoprotein-mediated efflux and enhance lymphatic drug transport through stimulation of lipoprotein and chylomicron production, consequently circumventing first-pass hepatic metabolism [163,169]. Beyond these intrinsic pharmacokinetic advantages, liquid SEDDS confer practical clinical benefits that enable weight-based dosing, ease of administration, and improved patient acceptability [12,149]. These advantages are particularly relevant for the growing pediatric TB population, where age-appropriate and suitable rifampicin TB formulations remain scarce yet urgently needed [17,37,46].

Despite reports of improved rifampicin solubility in fixed-dose combination SEDDS formulations containing isoniazid and rifampicin, no oral liquid rifampicin lipid-based formulations – such as SEDDSs – have yet been successfully developed or made commercially available. Evidence from literature indicates that, in separate studies, the solubility, physicochemical characteristics and formulation stability of rifampicin were improved when the drug was incorporated into SEDDSs based formulations [39,178]. Collectively, these findings emphasize the importance of excipient selection in the development of rifampicin SEDDSs [39,178].

In conclusion, the development of oral liquid rifampicin-based SEDDSs provides much more than a minor formulation adjustment. These drug delivery systems offer a strategic and scientific means to overcome the longstanding physicochemical barriers of rifampicin. By maintaining rifampicin in a stable and solubilized state throughout the gastrointestinal tract, liquid SEDDS formulations have the potential to deliver reliable, age-appropriate rifampicin therapy, narrowing established pediatric TB treatment disparities in high TB burden areas.

7. Conclusions

Pediatric TB endures as a underprioritized global health concern, where preventable morbidity and mortality continue to burden this vulnerable population [4]. This is further intified by the susceptibility of young children to TB progression and disseminated disease [60,64,65], diagnosing challenges [58], and shortcomings in pharmacotherapy [4]. Rifampicin, a cornerstone first-line TB drug, continues to face major challenges, such as a lack of rifampicin child-friendly dosage forms [50,51], physicochemical instabilities [106,112], and drug-drug interactions which further compromise its bioavailability [30,38,123]. These barriers often lead to inadequate dosing, poor treatment adherence, and an increased risk of drug resistance [29,37,90]. As emphasized in this review, there is a critical need for commercially available rifampicin child-friendly formulations to ensure effective and safe drug delivery and pharmacotherapy [53,146]. Liquid rifampicin SEDDSs offer a promising approach as they may enhance drug aqueous solubility, improve stability [162], increase gastro-intestinal absorption [175], and may potentially bypass first-pass hepatic metabolism [163,169]. These lipid-based delivery systems are scalable, feasible, and well suited for weight-based dosing, making them for the pediatric population, particularly those in low-resource settings [12,162,166]. Although no oral liquid rifampicin SEDDS has yet reached the market, advancing this promising approach could finally deliver a stable, child-friendly formulation filling the longstanding

void in pediatric TB treatment. As a focused examination of pediatric TB, this review is an imperative approach to emphasize the crucial need for sustained research and innovation to not only change the global trajectory of pediatric TB but also to drive decisive action.

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