RESEARCH PAPER

Coconut Oil-based SNEDDS Loaded with Rifampicin Improves Oral Bioavailability and Drug Safety

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ABSTRACT

Rifampicin (RIF) is a first-line antitubercular (anti-Tb) drug despite its decreased oral bioavailability and remarkable hepatotoxicity owing to its poor aqueous solubility. A coconut oil-based RIF-loaded self-nanoemulsifying drug delivery system (RF1) was developed beforehand to resolve the solubility issue. This work aimed to appraise the pharmacokinetic (PK) profiles and safety properties of RF1 for future endeavors. The comparative PK and safety profiles of pure RIF and the RF1 formulation were elucidated after oral administration to *Wistar* rats. In the PK study, blood sample was collected at definite time intervals from experimentally grouped animals orally administered raw RIF or RF1 at dose of 50 mg/kg body weight (b.w.). For the safety study, pure RIF and formulated RF1 were administered consecutively for fourteen days, dosed 50 and 125 mg/kg b.w. Twenty-four hours after final dose, the blood, liver, and kidney samples were amassed for biochemical analysis and histological characterization. RF1 revealed a 1.5-fold greater relative bioavailability (F) and a 1.4-fold greater C_{max} within 30 min (T_{max}) than did raw RIF, resulting in an improved $AUC_{0\text{-}480}$ of RF1, with a comparable mean residence time and elimination half-life of the drug, indicating its potential pharmacological efficacy. Moreover, the *in vivo* safety evaluation revealed RF1 as innocuous as pure RIF, as characterized by liver and kidney markers and corresponding histological observations. Based on the findings from PK and safety studies, the SNEDDS of RIF might be a potential alternative for delivering rifampicin orally and may improve bioavailability while minimizing toxicity.

Keywords: Tuberculosis, Coconut oil, Pharmacokinetic, Hepatotoxicity

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INTRODUCTION

Mycobacterium tuberculosis (Mtb) is the principal malefactor triggering airborne and highly contagious disease tuberculosis (TB). From the first discovery to date, TB is considered one of the top 10 deadliest infectious illnesses that lead to morbidity and mortality, especially in developing and under-developing countries. Moreover, multidrug-resistant TB has emerged as an alarming threat globally.[1-3] In contrast, only a limited number of drugs are available to effectively treat TB. The first-choice anti-TB drugs recommended by the WHO are rifampicin (RIF), isoniazid, pyrazinamide, and ethambutol.[4,5] Among these, RIF, the lead representative for combating TB, is a BCS-II drug associated with several therapeutic limitations due to poor aqueous solubility. Some studies have designated RIF as a BCS-IV drug because of its poor membrane permeability also.[6] In this context, researchers' foremost obligation is to increase the RIF's solubility and dissolution through various innovative formulation tactics. Numerous approaches, such as mucoadhesive rectal gels, liposomes, inclusion complexes, microspheres, nanocomposites, nanoparticles, and microparticles, have been reported to overcome the limited solubility issues associated with RIF. Among these approaches, nanoparticle-mediated oral delivery has gained considerable attention because of its ability to lift solubility and oral bioavailability, meanwhile reducing toxicity.[7-23] In addition, lipid-based self-nanoemulsifying drug delivery systems (SNEDDS) have focused on improved oral bioavailability, diminished plasma profile swings, and formulation adaptability with a broad-spectrum drug delivery method. The carriers that modify hydrophobic drugs such as SNEDDS are numerous natural, synthetic, and semisynthetic oils/lipids. Among these, natural vegetable oils are promising because of their ease of absorption, digestion, metabolism, and elimination. In addition, these oils are widely used as regular dietary components.[24-29] Despite this, pharmaceutical scientists

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have focused on presenting RIF through SNEDDS utilizing synthetic and semisynthetic oils/lipids only.

In some cases, natural oils, e.g., castor oil has been used for this purpose.[30-32] Coconut oil (CO), a common vegetable oil, has been used in Nigeria to treat TB.[33] The authors presumed that RIF, in combination with CO, would synergistically improve tuberculostatic activity through enhanced solubility.

Our previous study reported that the formulation of RIF-SNEDDS using CO resulted in faster and absolute drug release than did pure RIF. In addition, this formulation rapidly provided the *in vitro* minimum inhibitory concentration (MIC) for tuberculostatic activity within 30 min. In contrast, pure RIF failed throughout the entire study period (120 min), confirming the advantages of this newly developed formulation in terms of its drug release profile and *in vitro* MIC values.[34] However, it is necessary to investigate the pharmacokinetic and safety properties of this formulation before it can be used in clinical studies. Therefore, our study aimed to evaluate the pharmacokinetic parameters and *in vivo* safety markers of RIF-SNEDDS compared with those of pure RIF in a *Wistar* rat model.

MATERIALS AND METHODS

Materials

Novartis (Bangladesh) Limited kindly gifted rifampicin (Batch no: B625174). Acetonitrile (ACT), methanol (MET), and formic acid (FA) were LC-MS rating (purity>99.9%) and procured from Honeywell (Germany), and carboxymethyl cellulose sodium (CMC-Na) was purchased from Merck KGaA (Germany). Commercial kits to quantify serum glutamic pyruvic transaminase (SGPT), serum bilirubin (SBR), serum creatinine (SCr), total cholesterol (TC), and serum glutamic oxaloacetic transaminase (SGOT) were purchased from Elzzad Biosystem Pte Ltd. (Singapore) and Labkit (Barcelona, Spain), respectively. Every other chemical and reagent we used in our study was of LC-MS quality.

Preparation and *in vitro* evaluation of RIF-loaded SNEDDS (RFs)

In our previous work, a total of eighteen different formulations were developed.[34] However, we have focused specifically on three formulations. These were carefully selected and modified by varying the concentration to evaluate their performance as nano formulations. The primary objective was to investigate how different levels of coconut oil influenced the physicochemical characteristics, stability, and efficacy of the formulations. Through comprehensive analysis and comparative assessment, we were able to identify and optimize the most effective formulation among the three, demonstrating its potential for further *in vivo* development and application.

Briefly, the method involved the mixing of coconut oil, polysorbate-80, and ethanol at various weight ratios (Table 1) at 2400 rpm via a magnetic stirrer (78-1 Magnetic Stirrer Hotplate, China). The oil phase was then dispersed in water and evaluated visually to ensure clarity, homogeneity, and self-emulsification attributes. RIF was loaded into the transparent and homogeneous emulsion at a RIF: oil phase=1:100 ratio by mixing with a vortex (VIBROMIX 10, Slovenia) at 2850 rpm. The formulation RF1, under this study, was optimized on the basis of the drug release profile, size and morphology of globules, polydispersity index, zeta potential analysis, and *in vitro* tuberculostatic activity using minimum inhibitory concentration determination (MIC) against RIF-sensitive Mtb strains (ID1 and ID2).[34]

Table 1: Composition of various oil phases nanoemulsion.[34]

Formulation	Coconut oil (% weight)	Polysorbate-80 (% weight)	Ethanol (% weight)	Total (% weight)
NE1*	50	50	-	100
NE2	50	40	10	100
NE3	50	30	20	100

*Hereafter denoted as RF1 and subjected to *in vivo* evaluation

In vivo study of RIF-loaded SNEDDS (RF1)

Experimental animals

Thirty-five female *Wistar* rats (aged 8 weeks; weight: 180-220 g) were amassed from the Department of Pharmacy, Jahangirnagar University, Savar, Dhaka, and housed in the animal care centre of the Department of Pharmacy, University of Rajshahi, for 2 weeks before the commencement of study. The animals were supplied with standard food and liquid ad libitum for rodents. The animal care centre temperature was kept at 25±2˚C with a 12-hour cycle of light and dark throughout the study. *Wistar* rats were randomized by simple randomization method using random number generator to minimize bias. The animal study was performed following an approved protocol (Serial no.: 0008, date of approval: 21 November, 2024) by the Institutional Animal, Medical Ethics, Biosafety, and

Biosecurity Committee (IAMEBBC) of the Institute of Biological Sciences (IBSc), University of Rajshahi, based on the principle of the World Medical Association (WMA) Declaration of Helsinki. The Committee's approved document's Memo No. is 176/320(61)/IAMEBBC/IBSc).

Analytical method

To quantify plasma RIF concentration, we developed a method using an LC-MS/MS (SCIEX, Triple Quad 7500) system.[35] The LC arrangement used in this study was fitted with a C-18 column (Kinetex, 150×2.1 mm, 2.6 µm). We used a mobile phase consisting of ACT containing 0.1% v/v FA and 10 mM Ammonium Acetate buffer (pH 5) for the chromatographic separation. For complete elution, each sample was run for 7 min at a flow rate of 0.4 ml/min, having an injection volume of 10 µl. The gradient throughout the run was 5% ACT from 0 to 1.5 min, increasing to 98% ACT from 1.5 to 5.1 min, and finally reverting to 5% ACT from 5.1 to 7 min. For the validation of the method, we constructed a standardization curve using a concentration range of 0.2-10 µg/mL of pure RIF spiked with blank plasma that showed the linearity value $R^2 = 0.9997$.

Pharmacokinetic study of RF1

The acclimatized rats were split into two groups, each containing five (Table 2). After overnight fasting (12 h), a single dose of pure RIF or engineered RF1 (50 mg/kg b.w.) was orally administered to each rat.[36] Following pentobarbital (30 mg/kg, i.p.) anesthesia, blood sample (200 µl) was collected from the tail vein of each experimental rat in heparinized tubes at 0, 5, 15, 30, 60, 120, 240, and 480 min, and instantly centrifuged at 5000×g (Centurion, UK) for 10 min to isolate the plasma.[37] Specifically, 50 µl plasma was taken to eppendorf tube, to which 450 µl of ACT was added, followed by vortexed instantly for 10 sec, allowing protein precipitation and centrifuged for 5 min at 5000×g. The collected supernatant was filtered by a 0.2 µm nylon filter and transferred into the sample vial to estimate the plasma concentration of RIF via LC-MS/MS.

The PK parameters, i.e., peak plasma concentration (C_{max}), time to reach peak concentration (T_{max}), area under the curve (AUC_{0-480}), plasma half-life ($T_{½}$), mean residence time (MRT), and relative bioavailability (F), were determined via PK Solver 2.0, an add-in program in Microsoft Excel.[38]

Safety evaluation of RF1

The rats were split into five groups, with five rats in each. They were subjected to the specified doses (50 mg/kg b.w. and 125 mg/kg b.w.) of pure RIF, RF1, or vehicle only (as mentioned in Table 2) for 14 consecutive days.[36,39,40] Twenty-four hours after the last dose, following pentobarbital (30 mg/kg, i.p.) anesthesia,[37] blood sample was taken from the jugular vein of rat in premixed clot activator tubes. The blood was centrifugated for 10 min at 5000×g, and plasma was collected for biochemical analysis (SGPT, SGOT, SBR, SCr, and TC) immediately via a HumaLyzer 3000 (HUMAN).

Liver and kidney were collected and preserved in buffered formalin (10% v/v formalin solution with citrate buffer at pH 7.0). Fixed sections of the organs were cut to a 5 µm thickness. Following p-xylene deparaffinization, the tissue sections were rehydrated using varying isopropanol concentrations (descending grade) and washed with running water. The slide was stained with hematoxylin, counterstained with eosin, cover-slipped, and examined under a microscope fitted with a digital camera.[41]

Table 2: Grouping of rats for *in vivo* experiments (pharmacokinetic and safety assessment).

Features	Group	Dose administered
PK study	RIF	Pure RIF 50 mg/kg b.w. (single dose)
	RF1	RF1 equivalent to pure RIF 50 mg/kg b. w. (single dose)
Safety evaluation	NC	Vehicle only (once daily for 14 days)
	RIF-L	Pure RIF 50 mg/kg b. w. (once daily for 14 days)
	RIF-H	Pure RIF 125 mg/kg b. w. (once daily for 14 days)
	RF1-L	RF1 equivalent to pure RIF 50 mg/kg b. w. (once daily for 14 days)
	RF1-H	RF1 equivalent to pure RIF 125 mg/kg b. w. (once daily for 14 days)

Statistical analysis

Microsoft Excel-2024 and Graph Pad Prism (San Diego, CA; 10.2.2) were used to analyze the data and construct the graphs. The values are the means with standard error mean (S.E.M). A one-way ANOVA followed by Tukey's post-hoc test were employed to compare the differences among groups. In contrast, two groups were differentiated via Student's t-test. The p-value of 0.05 or lower was deemed significant statistically.

RESULTS AND DISCUSSION

***In vitro* evaluation of RIF-loaded SNEDDS (RF1)**

RF1 was identified as a type B emulsion based on visual observations. It exhibited a 6.2-fold increase in drug release *in vitro* at 5 min compared to pure RIF. The average size of globules was 230.2 ± 33.2 nm, and the zeta potential was -79.2 mV, indicating a stable RIF-loaded SNEDDS. Furthermore, the polydispersity index was 0.768, and transmission electron microscopy analysis (Figure 1) confirmed the homogeneous dispersion of the formulation. A tuberculostatic activity study was performed against two species, ID1 (MIC 1.0 μg/ml) and ID2 (MIC 0.5 μg/ml), of Mtb. The dissolution samples of pure RIF showed no time-dependent inhibition of growth in the aforesaid Mtb species till 120 min, while RF1 demonstrated inhibition at 30 and 45 min, respectively.[34]

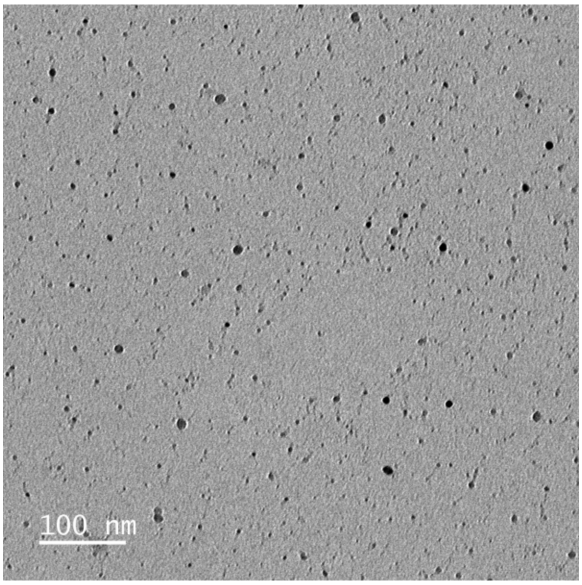

Figure 1: Transmission Electron Microscopic images of RF1.

In vivo pharmacokinetic (PK) study

The *in vivo* PK markers assess a drug's absorption, distribution, and elimination pattern when released from a specific dosage form. Hence, a steadfast approach is required to determine the relationship betwixt *in vitro* release and *in vivo* PK properties of drugs. As a new formulation, RF1 was developed with improved *in vitro* drug release properties, as shown in our previous report, and a PK study of this formulation was performed in comparison with that of pure RIF. The values of various PK parameters for the RIF and RF1 groups are presented in Table 3. In addition, Figure 2 displays the comparative PK profiles constructed with the plasma drug concentration versus time.

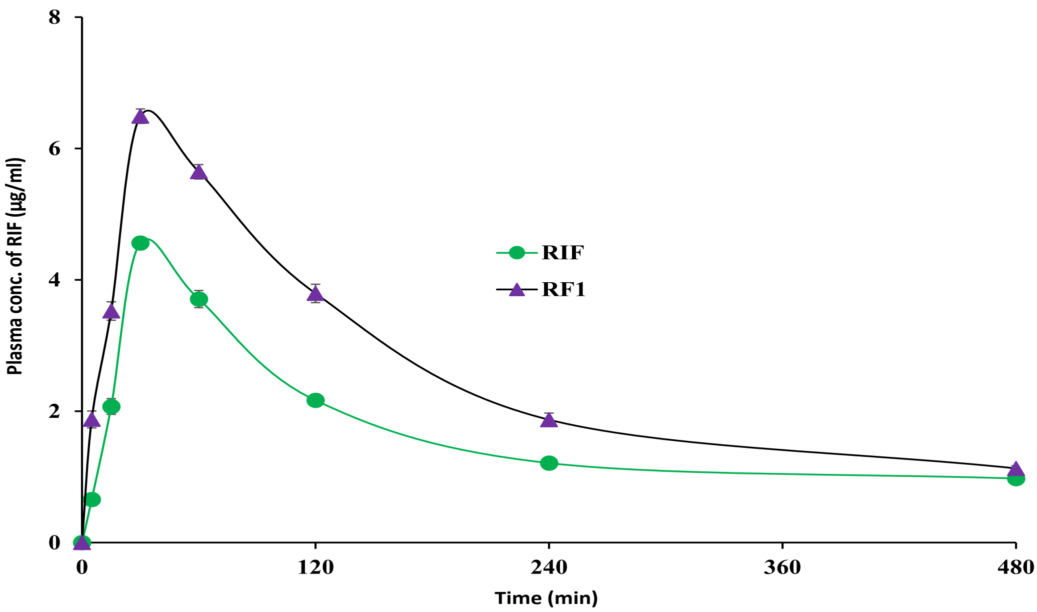

Figure 2: Plasma concentration-time profiles of rifampicin in rats following oral administration of a single dose of 50.0 mg/kg pure rifampicin in the RIF (closed circles) and RF1 (triangles). The results are presented as the mean ± S.E.M. (n = 5).

Table 3: Pharmacokinetic parameters of rifampicin after a single oral administration of pure RIF or RF1 formulation in the *Wistar* rat model. The results are presented as the mean ± S.E.M. (n = 5).

PK parameters	RIF Group	RF1 Group
C_{max} (μg/mL)	4.56±0.08	6.49±0.11
AUC_{0-480} (μg.min/mL)	829.96±30.37	1272.21±25.37
T_{max} (min)	30	30
$T_{1/2}$ (min)	206.31±9.30	185.24±3.98
MRT (min)	330.80±16.10	274.71±2.24
K_{el} (min^{-1})	0.0033	0.0037
F	1.0	1.5

In the RF1 group, the peak plasma concentration (C_{max}) of RIF was improved by 1.4-fold compared with that in the RIF group, indicating enhanced absorption followed by rapid onset of pharmacological action. According to the results of the noncompartmental analysis, the AUC_{0-480} values obtained from the RF1 group revealed a 1.5-fold greater bioavailability than did those of the RIF group, confirming their relative bioavailability (F values).

This significant ($p<0.05$) improvement in bioavailability by RF1 may be due to the formation of nanometric globules via the self-nanoemulsification technique, resulting in faster dissolution and accelerated permeability of RIF.[31,32,36,38,42]

These modifications in C_{max} and AUC_{0-480} are worthy of previously developed formulations, such as RIF-loaded microspheres and nanoparticles.[43,44] $T_{1/2}$ and MRT of RF1 were optimal, as shown in Table 3, which provided its greater margin of safety and efficacy.

Biochemical analysis of organ markers

As the liver is a vital organ for the metabolism of RIF, liver toxicity is one of the key drawbacks of this drug. Previous reports have indicated a certain degree of hepatotoxicity and nephrotoxicity associated with RIF therapy.[45,46,47] As a result, ensuring the safety of our new formulation became essential. This study analyzed the comparative impact of RF1 and RIF on SGPT, SGOT, SBR, SCr, and TC as detailed in Table 4.

Table 4: Biochemical parameters of the treated groups after dosing for 14 consecutive days. The results are presented as the mean ± S.E.M. (n = 5).

Groups	SGPT (U/L)	SGOT (U/L)	SBR (mg/dL)	SCr (mg/dL)	TC (mg/dL)
NC	18.50±4.43	15.00±0.63	0.75±0.03	0.50±0.00	218.50±2.84
RIF-L	58.50±11.07**	32.50±6.01*	1.55±0.03***	0.40±0.00	226.50±6.32
RIF-H	59.00±6.7**	33.50±1.57*	1.40±0.04***	0.40±0.04	208.50±4.25
RF1-L	51.00±7.59	32.50±2.84*	0.90±0.06	0.50±0.06	224.50±4.74
RF1-H	60.67±6.39**	39.67±5.18**	1.43±0.11***	0.47±0.03	215.00±14.96

*p≤0.05 vs NC; **p≤0.01 vs NC; ***p≤0.0001 vs NC; #p≤0.05 vs RIF-L; ##p≤0.01 vs RIF-L; ###p≤0.0001 vs RIF-L; @p≤0.05 vs RIF-H; @@p≤0.01 vs RIF-H; @@@p≤0.0001 vs RIF-H.

Administration of RIF and RF1 at low and high doses for 14 consecutive days, increased SGPT significantly ($p\leq0.01$) in the RIF-L, RIF-H, and RF1-H groups in compared to that of NC group. However, lower SGPT level was observed in RF1-L treated group than that of RIF groups. In addition, all the treated groups presented significant increase of SGOT levels compared to NC group. A significant increase in SBR was observed in RIF-L ($p\leq0.0001$), RIF-H ($p\leq0.0001$), and RF1-H ($p\leq0.0001$) groups except in RF1-L, which was concordant with that of SGPT data, suggesting that hepatic injury caused by the formulation (RF1) would be less accountable than that of RIF groups.

SCr is one of the key markers of kidney function.[48] SCr levels in experimental groups such as RIF-L (0.40 mg/dL), RIF-H (0.40 mg/dL), RF1-L (0.50 mg/dL), and RF1-H (0.47 mg/dL) did not significantly differ from that of NC group (0.50 mg/dL) suggesting that the formulation RF1 would keep away from nephrotoxicity.

Histological studies of the liver and kidneys

Liver tissues of NC group appeared normal cellular histology with well-defined hepatocytes (Figure 3A(i)). In contrast, the hepatocytes in RIF-treated groups (Figure 3A (ii & iii)) presented various abnormalities, including swelling and mild inflammation. Similar observation was also reported earlier that RIF therapy notably impacts on the development of liver toxicity.[7,47,49] Besides, the morphology of hepatocytes in RF1 treated groups (Figure 3A (iv & v)) was observed similar to that of NC group indicating the formulation RF1 being safer than pure drug.

The histological analysis of kidneys (Figure 3B) across all treatment groups revealed no cellular or morphological abnormalities, confirming the safety of the RIF-loaded SNEDDS formulation regarding nephritic alterations. Therefore, as noted in previous studies decreasing the dosage of RIF may be an approach.[36,50]

Estimation of total cholesterol levels

The serum TC level was measured as an extra safety indicator for RF1 formulated with CO. At the end of treatment, TC level did not significantly vary between the treatment and NC groups (Table 4). The results were concordant with the liver histology, revealing no signs of lipid accumulation (Figure 3A (iv-v)). Thus, the possibility of abnormalities can be overcome in long-term treatment with the proposed formulation RF1. Also, CO is regarded as FDA-approved "Generally Recognized as Safe (GRAS)" and a pharmaceutical excipient showing a negligible risk of accumulating as a fatty mass.[25, 51-54]

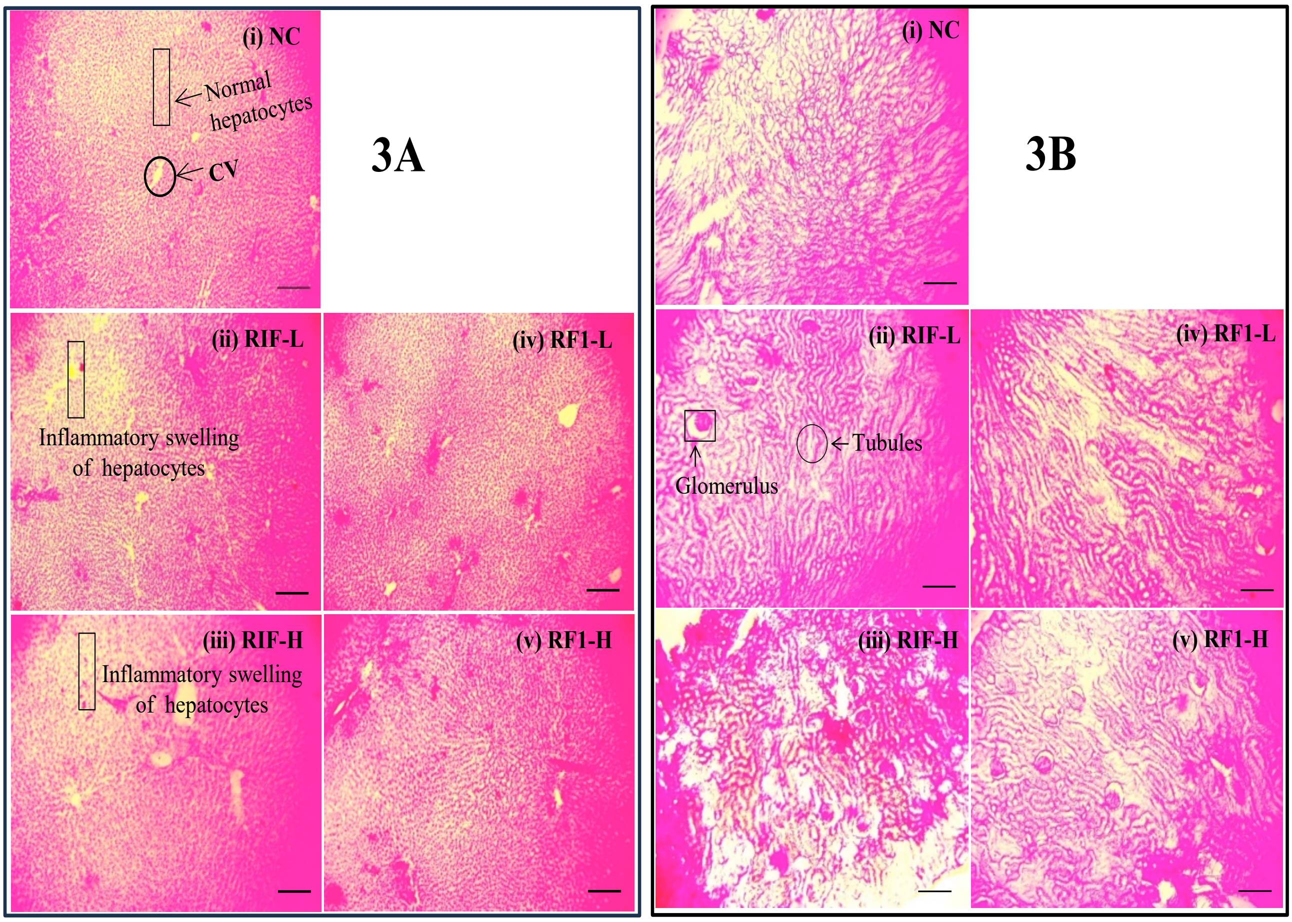

Figure 3: Histology of liver (3A) and kidney (3B) tissues of experimental rats. Tissues were stained with hematoxylin and eosin, viewed under a light microscope (Olympus IX71, Japan) with 10× magnification connected to a computer. The representative photographs are: (i) NC group received vehicle only; (ii) RIF-L group received 50 mg/kg pure RIF; (iii) RIF-H group received 125 mg/kg pure RIF; (iv) RF1-L group received the nanoemulsion eqv. to 50 mg/kg RIF; (v) RF1-H group received the nanoemulsion eqv. to RIF 125 mg/kg body weight daily. The scale bar represents 100 µm.

CONCLUSIONS

Our study aimed to overcome the main drawbacks, e.g., inadequate bioavailability and hepatotoxicity resulting from the poor aqueous solubility of rifampicin, the principal antituberculosis agent. The proposed self-nanoemulsifying drug delivery system has proven beneficial over other formulation techniques to overcome solubility issues with this simple and commercially economic scale-up technique. In this investigation, an SNEDDS loaded with RIF was formulated using coconut oil, a common and inexpensive natural vegetable oil. The outcomes led us to different assumptions, including the enhanced absorption and relative bioavailability of RIF compared with those of pure RIF, without altering drug-related toxicity. Overall, the findings of our study believe that RIF-loaded SNEDDS can be an alternative drug delivery approach to replace existing SNEDDS.

ETHICS STATEMENT

The animal study was performed following an approved protocol (Serial No.: 0008, date of approval: 21 November, 2024) by the Institutional Animal, Medical Ethics, Biosafety, and Biosecurity Committee (IAMEBBC) of the

Institute of Biological Sciences (IBSc), University of Rajshahi, based on the principle of the World Medical Association (WMA) Declaration of Helsinki. The Committee's approved document's Memo No. is 176/320(61)/IAMEBBC/IBSc).

CONFLICT OF INTEREST

The authors declare no competing interests.

FUNDING STATEMENT

No

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REFERENCES

1. Pai M, Behr MA, Dowdy D, et al. Tuberculosis. *Nature Reviews Disease Primers*. 2016;2:16076. doi:10.1038/nrdp.2016.76.
2. Agyeman AA, Ofori-Asenso R. Tuberculosis—an overview. *Journal of Public Health and Emergency*. 2017;1:7. doi:10.21037/jphe.2016.12.08.
3. World Health Organization. *Global tuberculosis report 2020*. Available at: https://www.who.int/publications/i/item/9789240013131 (accessed 19.12.2024).
4. Alsayed SSR, Gunosewoyo H. Tuberculosis: Pathogenesis, current treatment regimens and new drug targets. *International Journal of Molecular Sciences*. 2023;24:5202. doi:10.3390/ijms24065202.
5. Gilpin C, Korobitsyn A, Migliori GB, Raviglione MC, Weyer K. The World Health Organization standards for tuberculosis care and management. *European Respiratory Journal*. 2018;51:1800098. doi:10.1183/13993003.00098-2018.
6. Moretton MA, Chiappetta DA, Sosnik A. Cryoprotection, lyophilization and physical stabilization of rifampicin-loaded flower-like polymeric micelles. *Journal of the Royal Society Interface*. 2012;9:487–502. doi:10.1098/rsif.2011.0414.
7. Al-Joufi F, Elmowafy M, Alruwaili NK, et al. Mucoadhesive in situ rectal gel loaded with rifampicin: Strategy to improve bioavailability and alleviate liver toxicity. *Pharmaceutics*. 2021;13:336. doi:10.3390/pharmaceutics13030336.
8. Rinaldi F, Hanieh PN, Sennato S, et al. Rifampicin-liposomes for *Mycobacterium abscessus* infection treatment: Intracellular uptake and antibacterial activity evaluation. *Pharmaceutics*. 2021;13:1070. doi:10.3390/pharmaceutics13071070.
9. Patil JS, Devi VK, Devi K, Sarasija S. A novel approach for lung delivery of rifampicin-loaded liposomes in dry powder form for the treatment of tuberculosis. *Lung India*. 2015;32:331–338. doi:10.4103/0970-2113.159559.
10. Manca ML, Sinico C, Maccioni AM, Diez O, Fadda AM, Manconi M. Composition influence on pulmonary delivery of rifampicin liposomes. *Pharmaceutics*. 2012;4:590–606. doi:10.3390/pharmaceutics4040590.
11. Anjani QK, Domínguez-Robles J, Utomo E, et al. Inclusion complexes of rifampicin with native and derivatized cyclodextrins: In silico modeling, formulation, and characterization. *Pharmaceuticals*. 2022;15:20. doi:10.3390/ph15010020.
12. Patil JS, Suresh S. Physicochemical characterization, in vitro release and permeation studies of respirable rifampicin-cyclodextrin inclusion complexes. *Indian Journal of Pharmaceutical Sciences*. 2009;71:638–643. doi:10.4103/0250-474X.59545.
13. Mwila C, Walker RB. Improved stability of rifampicin in the presence of gastric-resistant isoniazid microspheres in acidic media. *Pharmaceutics*. 2020;12:234. doi:10.3390/pharmaceutics12030234.
14. Mei Q, Luo P, Zuo Y, et al. Formulation and in vitro characterization of rifampicin-loaded porous poly(ε-caprolactone) microspheres for sustained skeletal delivery. *Drug Design, Development and Therapy*. 2018;12:1533–1544. doi:10.2147/DDDT.S163005.
15. Bhise SB, More AB, Malayandi R. Formulation and in vitro evaluation of rifampicin loaded porous microspheres. *Scientia Pharmaceutica*. 2010;78:291–302. doi:10.3797/scipharm.0910-09.
16. Mehanna MM, Mohyeldin SM, Elgindy NA. Rifampicin-carbohydrate spray-dried nanocomposite: A futuristic multiparticulate platform for pulmonary delivery. *International Journal of Nanomedicine*. 2019;14:9089–9112. doi:10.2147/IJN.S211182.
17. Maretti E, Rustichelli C, Gualtieri ML, et al. The impact of lipid corona on rifampicin intramacrophagic transport using inhaled solid lipid nanoparticles surface-decorated with a mannosylated surfactant. *Pharmaceutics*. 2019;11:508. doi:10.3390/pharmaceutics11100508.

18. Gao Y, Zuo J, Bou-Chacra N, et al. In vitro release kinetics of antituberculosis drugs from nanoparticles assessed using a modified dissolution apparatus. *BioMed Research International*. 2013:136590. doi:10.1155/2013/136590.
19. Patel BK, Parikh RH, Aboti PS. Development of oral sustained release rifampicin loaded chitosan nanoparticles by design of experiment. *Journal of Drug Delivery*. 2013:370938. doi:10.1155/2013/370938.
20. Sung JC, Padilla DJ, Garcia-Contreras L, et al. Formulation and pharmacokinetics of self-assembled rifampicin nanoparticle systems for pulmonary delivery. *Pharmaceutical Research*. 2009;26:1847–1855. doi:10.1007/s11095-009-9894-2.
21. Rampacci E, Marenzoni ML, Chiaradia E, et al. In vitro performances of novel co-spray-dried azithromycin/rifampicin microparticles for *Rhodococcus equi* disease treatment. *Scientific Reports*. 2018;8:12149. doi:10.1038/s41598-018-30715-z.
22. Mizoe T, Ozeki T, Okada H. Application of a four-fluid nozzle spray drier to prepare inhalable rifampicin-containing mannitol microparticles. *AAPS PharmSciTech*. 2008;9:755–761. doi:10.1208/s12249-008-9109-x.
23. Patomchaiviwat V, Paeratakul O, Kulvanich P. Formation of inhalable rifampicin-poly(L-lactide) microparticles by supercritical anti-solvent process. *AAPS PharmSciTech*. 2008;9:1119–1129. doi:10.1208/s12249-008-9152-7.
24. Vergallo C. Nutraceutical vegetable oil nanoformulations for prevention and management of diseases. *Nanomaterials*. 2020;10:1232. doi:10.3390/nano10061232.
25. Preeti, Sambhakar S, Saharan R, et al. Exploring lipids for their potential to improve bioavailability of lipophilic drug candidates: A review. *Saudi Pharmaceutical Journal*. 2023;31:101870. doi:10.1016/j.jsps.2023.101870.
26. Weng T, Qi J, Lu Y, et al. The role of lipid-based nano delivery systems on oral bioavailability enhancement of fenofibrate, a BCS II drug: Comparison with fast-release formulations. *Journal of Nanobiotechnology*. 2014;12:39. doi:10.1186/s12951-014-0039-3.
27. Qureshi MJ, Mallikarjun C, Kian WG. Enhancement of solubility and therapeutic potential of poorly soluble lovastatin by SMEDDS formulation adsorbed on directly compressed spray dried magnesium aluminometasilicate liquid loadable tablets: A study in diet-induced hyperlipidemic rabbits. *Asian Journal of Pharmaceutical Sciences*. 2015;10:40–56. doi:10.1016/j.ajps.2014.08.003.
28. Bach A, Babayan VK. Medium-chain triglycerides: An update. *The American Journal of Clinical Nutrition*. 1982;36:950–962. doi:10.1093/ajcn/36.5.950.
29. Morakul B. Self-nanoemulsifying drug delivery systems (SNEDDS): An advancement technology for oral drug delivery. *Pharmaceutical Sciences Asia*. 2020;47:205–220. doi:10.29090/psa.2020.03.019.0121.
30. Buya AB, Witika BA, Bapolisi AM, et al. Application of lipid-based nanocarriers for antitubercular drug delivery: A review. *Pharmaceutics*. 2021;13:2041. doi:10.3390/pharmaceutics13122041.
31. Hussain A, Singha SK, Singha N, Verma PRP. In vitro–in vivo–in silico simulation studies of anti-tubercular drugs doped with self nanoemulsifying drug delivery system. *RSC Advances*. 2016;6:93147–93161. doi:10.1039/C6RA14122F.
32. Hussain A, Shakeel F, Singh SK, et al. Solidified SNEDDS for the oral delivery of rifampicin: Evaluation, proof of concept, in vivo kinetics, and in silico GastroPlus™ simulation. *International Journal of Pharmaceutics*. 2019;566:203–217. doi:10.1016/j.ijpharm.2019.05.061.
33. Ogbole OO, Ajaiyeoba EO. Traditional management of tuberculosis in Ogun State of Nigeria: The practice and ethnobotanical survey. *African Journal of Traditional, Complementary and Alternative Medicines*. 2009;7:79–84. doi:10.4314/ajtcam.v7i1.57270.
34. Ghosh MK, Khan MRI, Rony SR, et al. Design, optimization and in vitro assessment of rifampicin loaded self-nanoemulsifying drug delivery system. *Research Journal of Pharmacy and Technology*. 2025;18:2023–2031. doi:10.52711/0974-360X.2025.00289.
35. Karaźniewicz-Łada M, Kosicka-Noworzyń K, Rao P, et al. New approach to rifampicin stability and first-line anti-tubercular drug pharmacokinetics by UPLC-MS/MS. *Journal of Pharmaceutical and Biomedical Analysis*. 2023;235:115650. doi:10.1016/j.jpba.2023.115650.
36. Singh H, Jindal S, Singh M, Sharma G, Kaur IP. Nano-formulation of rifampicin with enhanced bioavailability: Development, characterization and in vivo safety. *International Journal of Pharmaceutics*. 2015;485:138–151. doi:10.1016/j.ijpharm.2015.02.050.
37. Leitão SAT, Soares DDS, Junior NC, Zimmer R, Ludwig NF, Andrades M. Study of anesthetics for

euthanasia in rats and mice: A systematic review and meta-analysis on the impact upon biological outcomes (SAFE-RM). *Life Sciences*. 2021;284:119916. doi:10.1016/j.lfs.2021.119916.

38. Mohsin K, Alamri R, Ahmad A, Raish M, Alanazi FK, Hussain MD. Development of self-nanoemulsifying drug delivery systems for the enhancement of solubility and oral bioavailability of fenofibrate, a poorly water-soluble drug. *International Journal of Nanomedicine*. 2016;11:2829–2838. doi:10.2147/IJN.S104187.
39. Kannabiran BP, Palaniappan NA, Manoharan T, et al. Safety and efficacy of 25 mg/kg and 35 mg/kg vs 10 mg/kg rifampicin in pulmonary TB: A Phase IIb randomized controlled trial. *Open Forum Infectious Diseases*. 2024;11:ofae034. doi:10.1093/ofid/ofae034.
40. OECD. *Guidelines for the Testing of Chemicals*. Available at: https://www.oecd.org/en/topics/sub-issues/testing-of-chemicals/test-guidelines.html.
41. Ghosh MK, Wahed MII, Khan RI, Habib A, Barman RK. Pharmacological screening of fenofibrate-loaded solid dispersion in fructose-induced diabetic rat. *Journal of Pharmacy and Pharmacology*. 2020;72:909–915. doi:10.1111/jphp.13267.
42. Gardouh A, Gamal A, Gad S. Formulation and pharmacokinetic evaluation of rifampicin solid lipid nanoparticles. *Journal of Research in Pharmacy*. 2020;24:539–551. doi:10.35333/jrp.2020.202.
43. Coowanitwong I, Arya V, Kulvanich P, Hochhaus G. Slow release formulations of inhaled rifampin. *The AAPS Journal*. 2008;10:342–348. doi:10.1208/s12248-008-9044-5.
44. Trousil J, Pavliš O, Kubíčková P, et al. Antitubercular nanocarrier monotherapy: Study of in vivo efficacy and pharmacokinetics for rifampicin. *Journal of Controlled Release*. 2020;321:312–323. doi:10.1016/j.jconrel.2020.02.026.
45. Ragusa J, Gonzalez D, Li S, Noriega S, Skotak M, Larsen G. Glucosamine/L-lactide copolymers as potential carriers for the development of a sustained rifampicin release system using *Mycobacterium smegmatis* as a tuberculosis model. *Heliyon*. 2019;5:e01539. doi:10.1016/j.heliyon.2019.e01539.
46. Beebe A, Seaworth B, Patil N. Rifampicin-induced nephrotoxicity in a tuberculosis patient. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*. 2015;1:13–15. doi:10.1016/j.jctube.2015.09.001.
47. Kim JH, Nam WS, Kim SJ, et al. Mechanism investigation of rifampicin-induced liver injury using comparative toxicoproteomics in mice. *International Journal of Molecular Sciences*. 2017;18:1417. doi:10.3390/ijms18071417.
48. Chmielewski M, Heimbürger O, Stenvinkel P, Lindholm B. Uremic toxicity. In: Kopple JD, Massry SG, Kalantar-Zadeh K, eds. *Nutritional Management of Renal Disease*. 3rd ed. Academic Press; 2013:49–77. doi:10.1016/B978-0-12-391934-2.00004-7.
49. Scheuer PJ, Lal S, Summerfield JA, Sherlock S. Rifampicin hepatitis: A clinical and histological study. *The Lancet*. 1974;303:421–425. doi:10.1016/S0140-6736(74)92381-2.
50. Stielow M, Witczynska A, Kubryn N, Fijałkowski L, Nowaczyk J, Nowaczyk A. The bioavailability of drugs—The current state of knowledge. *Molecules*. 2023;28:8038. doi:10.3390/molecules28248038.
51. Bunggulawa EJ, Lee Y, Lee Y. Design, optimization, and evaluation of a self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of parsley n-hexane fraction utilizing coconut oil as the oil phase. *Polymer Korea*. 2025;49:375–385. doi:10.7317/pk.2025.49.3.375.
52. Hosny KM, Alhakamy NA, Sindi AM, Khallaf RA. Coconut oil nanoemulsion loaded with a statin hypolipidemic drug for management of burns: Formulation and in vivo evaluation. *Pharmaceutics*. 2020;12:1061. doi:10.3390/pharmaceutics12111061.
53. Fayez SM, Elnahas OS, Fayez AM, El-Mancy SS. Coconut oil based self-nano emulsifying delivery systems mitigate ulcerogenic NSAIDs side effect and enhance drug dissolution: Formula optimization, in vitro, and in vivo assessments. *International Journal of Pharmaceutics*. 2023;634:122666. doi:10.1016/j.ijpharm.2023.122666.
54. Gao Y, Liu Y, Han X, et al. Coconut oil and medium-chain fatty acids attenuate high-fat diet-induced obesity in mice through increased thermogenesis by activating brown adipose tissue. *Frontiers in Nutrition*. 2022;9:896021. doi:10.3389/fnut.2022.896021.