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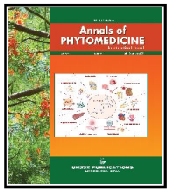

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Development of a novel self-nanoemulsifying drug delivery system (SNEDDS) for enhanced efficacy of bedaquiline

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Abstract

The clinical use of bedaquiline (BDQ) for treating MDR-TB is limited due to its poor dissolution and oral bioavailability. The bedaquiline-loaded self-nanoemulsifying drug delivery system (BDQ-SNEDDS) was prepared by simple admixture method. Based on maximum drug solubility, capryol 90, cremophor EL, and carbitol were chosen as the components for the self-nanoemulsifying drug delivery system (SNEDDS) formulation. Six formulations were prepared and optimized using various ratios of the selected excipients, including distilled water as the aqueous phase. Dynamic light scattering (DLS) results showed that the optimized formulations F1-F6 had particle sizes under 200 nm after 11 h of stirring. Bedaquiline loaded SNEDDS had a negative zeta potential of -21.16 ± 3.4 mV. Furthermore, above formulations were subjected to stability study and consequently formulation F5 was selected for further analysis due to its demonstrated stability. The inhibition diameter zones obtained by the well diffusion method for *Escherichia coli* and *Pseudomonas aeruginosa* demonstrated notable antibacterial activity of the BDQ-SNEDDS formulation. SNEDDS could be a potential candidate for enhanced efficacy of bedaquiline.

1. Introduction

The global rise in antibiotic-resistant tuberculosis (TB) is an increasing concern. The emergence of strains resistant to standard antibiotic treatments exacerbates the difficulty of controlling its spread and effectively treating patients (Pandey *et al*., 2014; Ugwu *et al*., 2020). This resistance not only complicates treatment protocols but also leads to longer, more expensive, and less successful treatment courses (Abdelsalam *et al.,* 2024; Kushwaha *et al*., 2023). Consequently, the development of new drugs and effective drug delivery strategies are crucial to combating this growing threat and reducing the burden of TB worldwide. Bedaquline (BDQ), a novel diarylquinoline antibiotic that acts as inhibitor of ATP synthtase for the treatment of MDR-TB (Andries *et al*., 2005). Bedaquiline can effectively eradicate M. tuberculosis in both dormant and actively growing forms, distinguishing it from antibiotics that target only actively growing bacteria, like protein-synthesis inhibitors (Hoagland *et al*., 2016). Bedaquiline treatment for MDR-TB has shown promising outcomes in both preclinical and clinical investigations. Bedaquiline, administered alone or with other anti-TB medications like pyrazinamide and moxifloxacin, accelerated culture conversion in TB patients, potentially reducing treatment duration compared to conventional regimens (Chang *et al*., 2018). However, its clinical use is restricted due to its poor dissolution profile, which limits its bioavailability and therapeutic effectiveness (Pardhi *et al*., 2022). These challenges stress the need for innovative drug delivery systems to enhance the solubility and absorption of BDQ, ensuring that patients with MDR-TB can benefit from this promising treatment.

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Lipid-based drug delivery systems have the potential to enhance the apparent solubility and dissolving characteristics of several medicines. The fundamental objective of these formulations is to preserve the solubility of drugs in the gastrointestinal system (Kesharwani *et al*., 2013). SNEDDS are lipid-based systems that have been intensively researched for the purpose of delivering drugs orally (Singh *et al*., 2022). Their small particle size, efficient production, enhanced stability, and excellent biocompatibility contribute to their popularity (Nasr *et al*., 2016). These systems typically include specific excipients such as oils, surfactants, and co-surfactants as components of the formulations (Rahman *et al*., 2012). After dissolving in water and gently shaking, SNEDDS form oil-in-water nanoemulsions with droplets usually 200 nm or smaller (Buya *et al*., 2020). Lipid components and surfactants in SNEDDS work together to improve the gastrointestinal tract's absorption of pharmaceuticals, and they can be tailored to accommodate both hydrophilic and hydrophobic medications (Morakul, 2020). Compared to other lipid carriers such as liposomes, solid lipid nanoparticles, nanoemulsions, and nanostructured lipid carriers, SNEDDS uses less energy for manufacturing and dispersion (Singh, 2021). Furthermore, when distributed in an aqueous phase, SNEDDS demonstrates excellent kinetic stability as well as great physical stability during storage (Patel *et al*., 2015). In light of the aforementioned, the project attempts to create and describe a unique SNEDDS in order to enhance its oral absorption and dissolution profile. Due to their excellent drug solubility, capryol 90, cremophor EL, and carbitol were selected (Rahman *et al*., 2013). Six formulations were optimized using different ratios of these excipients, with distilled water as the aqueous phase.

2. Materials and Methods

2.1 Chemical and reagentsm

The complimentary sample of bedaquiline was acquired from a pharmaceutical company. Colorcon Asia (Mumbai, India) generously

sent a free sample of propylene glycol monocaprylate (capryol 90) from gattefosse (France). Polyoxy-35-castor oil (cremophor EL) and diethylene monoglycol ether (carbitol) were obtained from Sigma Aldrich and Merck Limited, respectively. Merck India Ltd. supplied tween 80 and distilled water. Throughout the whole process, double-distilled water (DDW) was utilized. All remaining chemicals and solvents were of analytical grade.

2.2 Solubility of bedaquiline in different excipients

The solubility of bedaquiline in different excipients was evaluated in order to determine the suitable oil phase, surfactant, and co-surfactant for the formulation of SNEDDS. The maximum loading capacity of SNEDDS is determined by the drug's ability to dissolve in oils, surfactants, and co-surfactants. The screening components consisted of various oils (olive oil, labrafil M2125 CS, capryol-90), surfactants (cremophor EL, tween-80, solutol HS15), and co-surfactants (carbitol, polyethylene glycol-400). An excess quantity of bedaquiline was taken into different oils, surfactants, and co-surfactants, and placed in a temperature-controlled shaker for duration of 72 h at a constant temperature of 25 ± 2°C. Once equilibrium was achieved, the samples underwent centrifugation at a speed of 3000 revolutions per minute for a duration of 15 min. Subsequently, the liquid portion above the sediment, known as the supernatant, was passed over a membrane with a pore size of 0.45 µm in order to eliminate any medicines that were not soluble. The concentration of bedaquiline was measured using high performance liquid chromatography (HPLC). The excipients included for the formulation were all generally regarded as safe (GRAS) and selected based on the greatest solubility of bedaquiline (Ahmad *et al*., 2017).

2.3 Development of bedaquiline SNEDDS formulations

The SNEDDS was prepared by combining oil, surfactant, and co-surfactant, using a technique based on the one developed with some minor modifications (Ren *et al*., 2013). Table 1 displays the preparation of six distinct SNEDDS formulations. A combination of several surfactants and co-surfactants was mixed in a specific ratio with the oil phase (containing the drug) and heated above their individual melting temperatures. This was done to ensure that the mixture was completely dispersed and to avoid any residual lipid effects. The aqueous phase was created by dissolving DMSO (2% v/v) in distilled water and the volume was then adjusted to 100 ml. Subsequently, a solution of bedaquiline, with a concentration of 5 mg/ml and dissolved in the oil phase, was slowly added to the formulation. The mixture was then mixed at room temperature for duration of 72 h, while being continuously monitored. Following the synthesis process, the SNEDDS underwent filtration and was instantly put into a glass vial for further analysis to detect any alterations.

Table 1: Composition of self-nanoemulsifying drug delivery system (SNEDDS) formulations

Excipients	Formulations (% v/v)					
	F1	F2	F3	F4	F5	F6
Capryol 90	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Cremaphor EL	1 ml	2.5 ml	3 ml	3.5 ml	4 ml	5 ml
Carbitol	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Drug	1 mg/ml	2 mg/ml	2.5 mg/ml	3 mg/ml	5 mg/ml	5 mg/ml
Distilled water	6 ml	4.5 ml	4 ml	4 ml	3.5 ml	2 ml

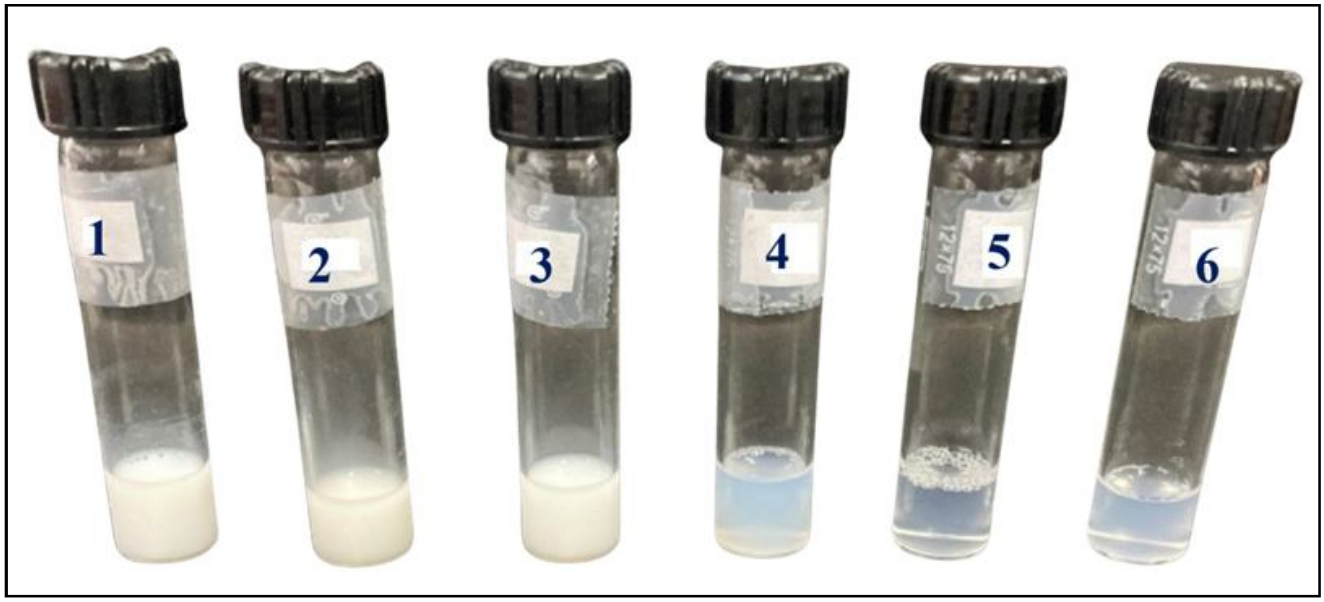


Figure 1: Aliquots for the optimized BDQ-SNEDDS were prepared which were subjected to weekly assessment of droplet size to evaluate their stability over time.

2.4 Thermodynamic stability study

The selected formulations underwent several thermodynamic stability experiments to assess their physical stability. In the centrifugation test, a predetermined amount of each formulation was mixed with water at ratios varying from 1:10 to 1:100. The mixture was then subjected to centrifugal force at a speed of 15,000 revolutions per minute for duration of 15 min. The formulations underwent visual inspection to detect any occurrence of phase separation. Afterwards, the formulations underwent freeze-thaw cycles ranging from -21°C to + 25°C, with storage at each temperature for a minimum of 48 h. The formulations that exhibited thermodynamic stability were chosen for additional analysis (Shafiq-un-Nabi *et al*., 2007).

2.5 Dispersibility test

A USP XXII dissolving device was used to assess the self-emulsification effectiveness (Rahman *et al*., 2012). One milliliter (1 ml) of each formulation was added to 500 milliliters of distilled water, 0.1 N HCl, and 6.8 phosphate buffer separately. The mixture was kept at 37 ± 1.0°C. A basic stainless steel dissolving paddle spinning at 50 rpm offered gentle agitation. The following grading system was used to classify and visually assess the formulations' *in vitro* performance (Table 2).

Table 2: Grading based on dispersibility test

Grade	Description
I	Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
II	Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
III	Bright white emulsion (similar to milk in appearance) formed within 2 min.
IV	Dull, grayish white emulsion with a slightly oily appearance that is slow to emulsify (longer than 2 min).

2.6 Stability studies

A study was conducted to assess the physical stability of BDQ-loaded SNEDDS. Stability was evaluated based on several characteristics, including phase separation, turbidity, and particle size. Inadequate dispersion stability may result in phase separation or precipitation, which would negatively affect the drug absorption and therapeutic efficacy. The investigation involved storing all BDQ-loaded SNEDDS formulations (F1-F6) at room temperature for several weeks. These formulations were extracted from storage at predetermined intervals (10 days, 20 days, and 30 days) and examined for any discernible changes in physical appearance, droplet size, and PDI. In this instance, we have studied particle size and phase separation over time (Flekka *et al*., 2024).

2.7 Analysis of drug content in SNEDDS

The best six formulations were chosen for examination, and their drug content was checked. Methanol was used to remove the medication from the SNEDDS formulations. The solutions obtained were passed through Whatman filter paper, which has a pore size of 0.45 µm. HPLC was then used to determine the drug content of the filtered solutions.

2.8 Dynamic light scattering (DLS) analysis

The zeta potential was measured using a zeta sizer. The average droplet size and polydispersity index (PDI) of the drug-loaded SNEDDS were calculated using dynamic light scattering (Dynpro-Tc-04 instrument, Protein Solution, Wyatt Technology). The hydrodynamic diameter mean was found using the Stokes-Einstein equation. At a 90° angle to the incoming beam, the intensity of the dispersed light was measured. The data was examined using the standard analytical method. The mean value of ten runs (conducted in duplicate) was taken into consideration for BDQ-SNEDDS size determination.

2.9 Fourier transform infrared spectroscopy (FTIR)

Utilizing fourier transform infrared spectroscopy (FTIR), the chemical makeup and structure of the recently synthesized drug-loaded SNEDDS were examined. FTIR spectroscopy measured the absorption and transmission of infrared radiation, which yielded important information regarding the functional groups present in the BDQ-SNEDDS. In addition to identifying chemical bonds and assisting in the understanding of molecular interactions, FTIR may also be used to classify unknown chemicals, detect contaminants, monitor chemical reactions, and assess sample quality.

2.10 Transmission electron microscopy (TEM)

TEM was used to optimize the morphological study of the obtained formulation. The sample preparation process was carried out in a particle-free, controlled atmosphere to guarantee precise results and prevent any size inconsistencies. The procedure is applying a copper grid to a paraffin sheet with forceps. Next, a thin layer of BDQ-loaded SNEDDS was carefully applied to the copper grid using a micropipette. The grid and sample were immersed in a 2% phosphotungstic acid solution to increase contrast. Extra fluid was removed by placing the copper grid on Whatman filter paper. The grid was exposed to a light beam when it had completely dried, and a transmission electron microscope was used to examine the droplet morphology.

2.11 *In vitro* drug release study

A study was undertaken to analyze the release of drugs from optimized self-nanoemulsifying drug delivery systems (SNEDDS) and pure drug suspension in a solution of 0.1 N HCl (pH 1.2). This was done using a pretreated dialysis bag with a molecular weight cut-off of 14,000 g/mole, obtained from Sigma, USA. 1 milliliter of the optimized self-nanoemulsifying drug delivery system (SNEDDS) and a suspension of pure medication were put into dialysis bags that had been prepared beforehand. These bags were then placed in two different 500 milliliter beakers that were filled with a solution of hydrochloric acid (HCl) with a concentration of 0.1 normal (N). Subsequently, the beakers were positioned on a magnetic stirrer, which was adjusted to a temperature of 37°C and a swirling speed of 100 rpm. 0.5 ml samples were taken at certain time intervals (2, 4, 6, 8, 10, and 12 h) and an equal volume of new dissolving medium was added to maintain the sink condition. The collected samples were

filtered using a 0.45 µm filter paper. The gathered samples were examined using high performance liquid chromatography (HPLC) to ascertain the concentration of the drug, and subsequently, the total amount of drug released was estimated (Balakumar *et al.,* 2013).

2.12 Antimicrobial potential of BDQ-SNEDDS

The antimicrobial activity of bedaquiline-loaded BDQ-SNEDDS was evaluated using the agar well diffusion method (Dahiya *et al.,* 2012).

2.12.1 Agar well diffusion method

In this assay, a specific amount of the BDQ-SNEDDS formulation was introduced into wells cut into agar plates inoculated with bacterial cultures. The plates were then incubated under appropriate conditions to allow bacterial growth. The antimicrobial potential was determined by measuring the diameter of the inhibition zones around the wells, indicating the effectiveness of the BDQ-SNEDDS formulation in inhibiting bacterial growth. This method provides a clear visual assessment of the antimicrobial efficacy of BDQ-SNEDDS compared to pure suspension of bedaquiline and placebo control. A sterile plastic spreader was used to evenly distribute a 100 µl aliquot of the suspended culture onto the petri dish, which was then incubated at 37°C. Wells were drilled into the agar plate following an hour of incubation. Then, an increasing volume of a normal antibiotic or drug-loaded SNEDDS (1 mg/ml stock solution) was added to each well of an agar plate. In order to calculate the zone of inhibition, the clear region surrounding each well that corresponded to the bacterial clearance mediated by BDQ-SNEDDS after 24 h was measured.

2.13 Statistical analysis

Statistical analysis was performed on SPSS software version 17.0. One-way analysis of variance (ANOVA) was used to determine the differences between groups. p value <0.05 was considered as statistically significant. All the results are expressed as a mean ± SD (n=3).

3. Results

3.1 Solubility and miscibility studies

Bedaquiline has highest solubility in Capryol 90 (380.60 ± 4.2), followed by Labrafil M 2125 CS (245 ± 6.00) as shown in Table 3. Based on the miscibility of surfactants and co-surfactants, Cremophor EL (surfactant) and Carbitol (co-surfactant) were selected as the formulation components that provided the highest transparency.

Table 3: Drug solubility and miscibility in various excipients

Solubility of bedaquiline in oils, surfactants and co-surfactants (mg/ml)		Surfactant and co-surfactant miscibility	
Olive oil	75.8 ± 6.9	**Surfactant**	**% Transparency**
Labrafil M2125 CS	245 ± 6.00	Cremaphor EL	100
Capryol 90	380.60 ± 4.2	Solutol HS15	92.4
Cremaphor EL	12 ± 2.14	Tween 80	65.5
Tween 80	6 ± 1.2	**Co-surfactant**	**% Transparency**
PEG 400	5 ± 1.9	PEG 400	99.4
Carbitol	8 ± 1.4	Carbitol	100

3.2 Formulation development and characterization

The composition of bedaquiline-SNEDDS in various formulations (F1, F2, F3, F4, F5 and F6) has been given in Table 1.

3.3 Stability study

Finally optimized BDQ-SNEDDS formulation F5 was assessed for stability on the basis of physical appearance, phase separation, droplet size, and PDI. Dynamic light scattering (DLS) results demonstrated that formulation F5 maintained a stable particle size over the month-long period, showing a particle size of 143.8 nm after 10 days and 148.9 nm after 30 days. These nearly similar particle sizes indicate that formulation F5 of the drug-loaded SNEDDS is stable over time. In contrast, the other formulations (F1, F2, F3, F4, and F6) did not maintain consistent particle sizes over the period, indicating instability (Figure 2). Consequently, formulation F5 was selected for further analysis due to its demonstrated stability.

3.4 Size distribution throughout the optimization process

Particle size characterization is a crucial aspect in the development of SNEDDSs, as it directly affects the performance of the medication in terms of absorption and stability. The size of the particles plays a significant role in both *in vivo* and *in vitro* evaluations of SNEDDSs. The size of the bedaquiline-loaded SNEDDS was determined using dynamic light scattering, which provided the average diameter of the droplets in the formulation (Figure 2). DLS provides insights into the kinetics of nanoparticle production by tracking changes in particle size distribution as the formulation process advances.

3.5 Zeta potential

The colloidal stability can be ascertained from the zeta potential. It is calculated by determining the droplets' electrophoretic mobility. Particle aggregation is less likely when there is a high zeta potential value because of repulsive electrostatic forces. As seen in Figure 4, bedaquiline loaded SNEDDS had a potential of -21.16 ± 3.4. The droplets' negative surface charge is shown by the negative zeta potential. A formulation is said to be stable when there is no coagulation and separation, also when the zeta potential value lies between -30 mv to +30 mv.

3.6 FTIR analysis

Using fourier transform infrared (FTIR) spectroscopy, the functional groups found in the BDQ SNEDDS were characterized.

Different chemical groups resulted in the formation of distinct peaks that corresponded to different wave numbers (Figure 5). We discovered C = C stretching vibrations of (the bands seen at 1638.17), C-N stretching vibrations of aromatic and aliphatic amines (the bands seen at 1012.62), and O-H stretching vibrations of hydroxyl groups (strong peaks at 2950-3350).

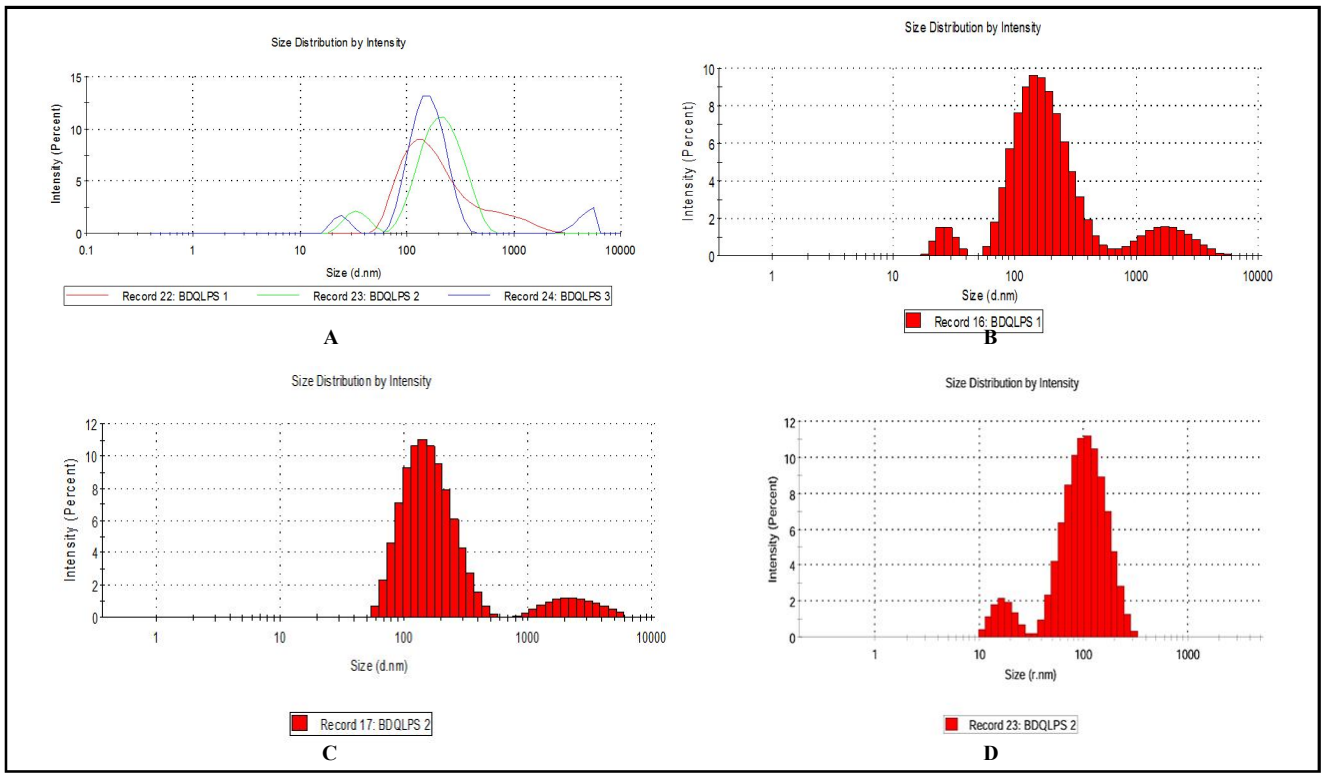
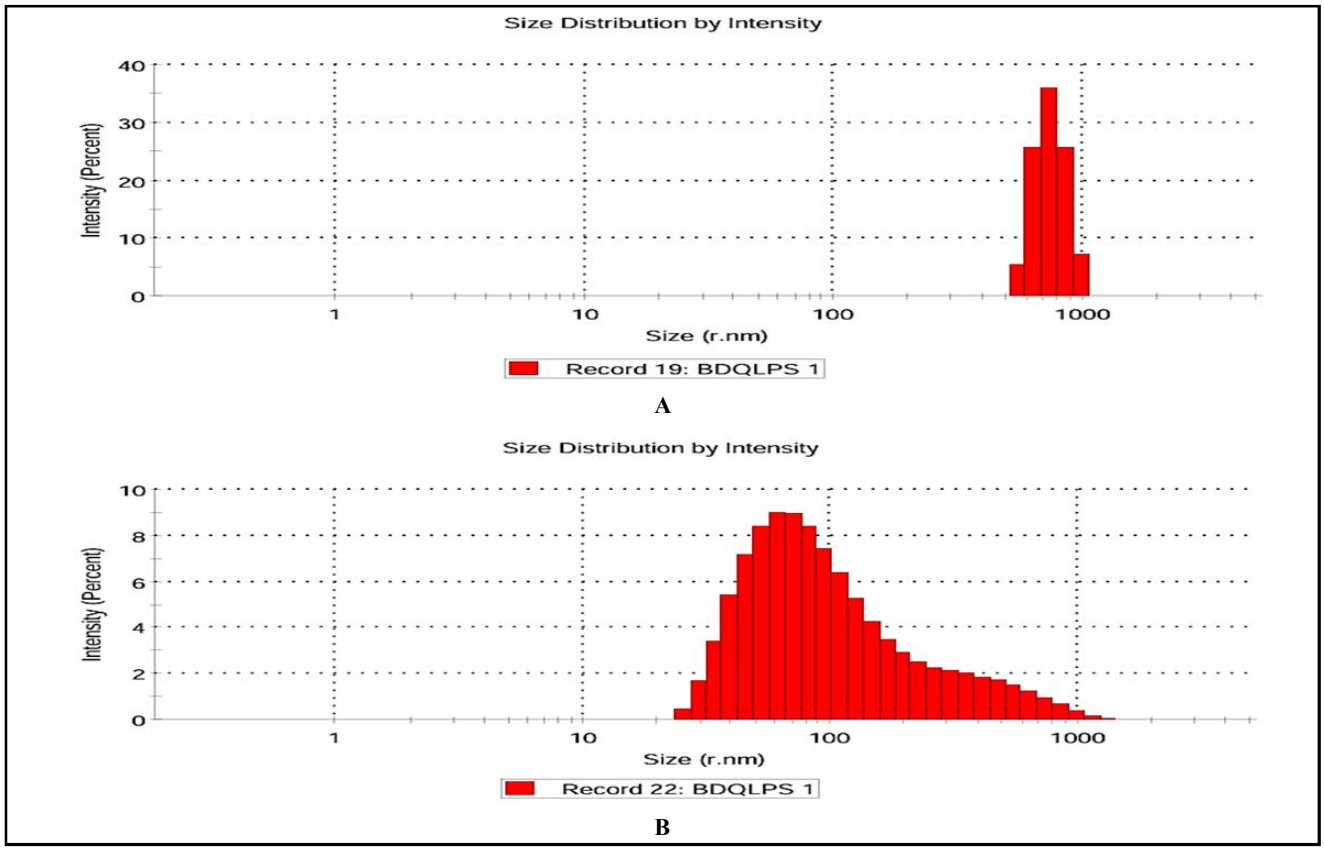


Figure 2: The graph displays the optimized BDQ-SNEDDS droplet's size when read on first weak (represented by blue), following second weak (red), and lastly third weak (green) showing a similar distribution of size over a time period, thus ensuring stability (A). The size distribution of optimized SNEDDS formulation (F5) depicts a similar intensity (B-D).



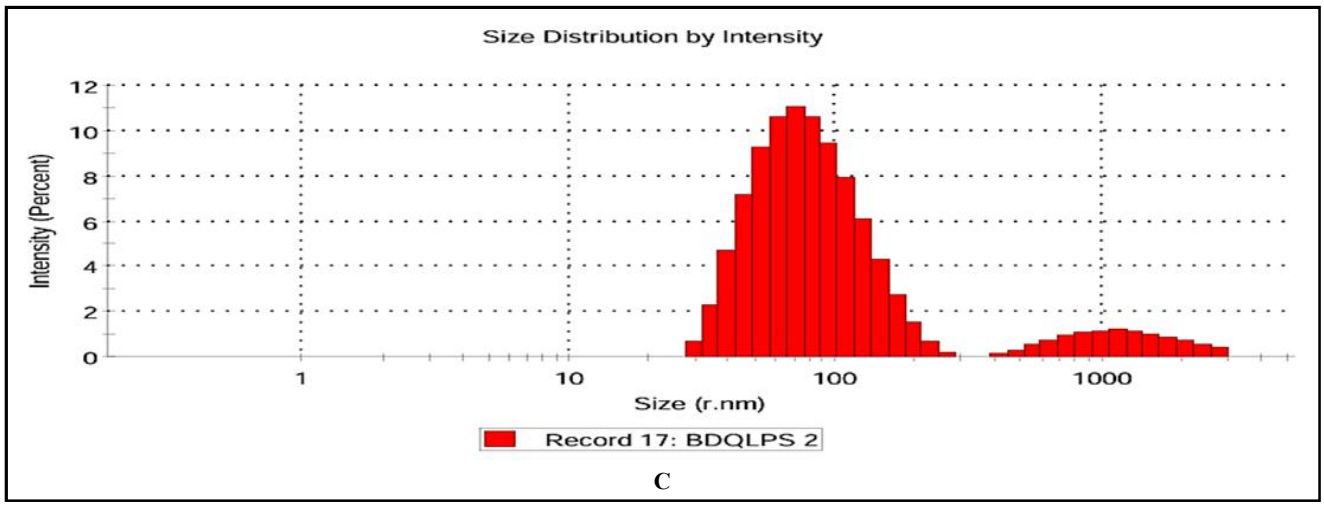


Figure 3: Graphical representation of droplet size and PDI throughout the optimization process of BDQ-SNEDDS. (A) Droplet in the range of 1000 nm with a PDI of 0.5 was obtained after 3 h of stirring, (B) 300-500 nm range with a PDI of 0.42 was obtained after 7 h of stirring, (C) 160 nm with a PDI of 0.3 was obtained after 11 h of stirring.

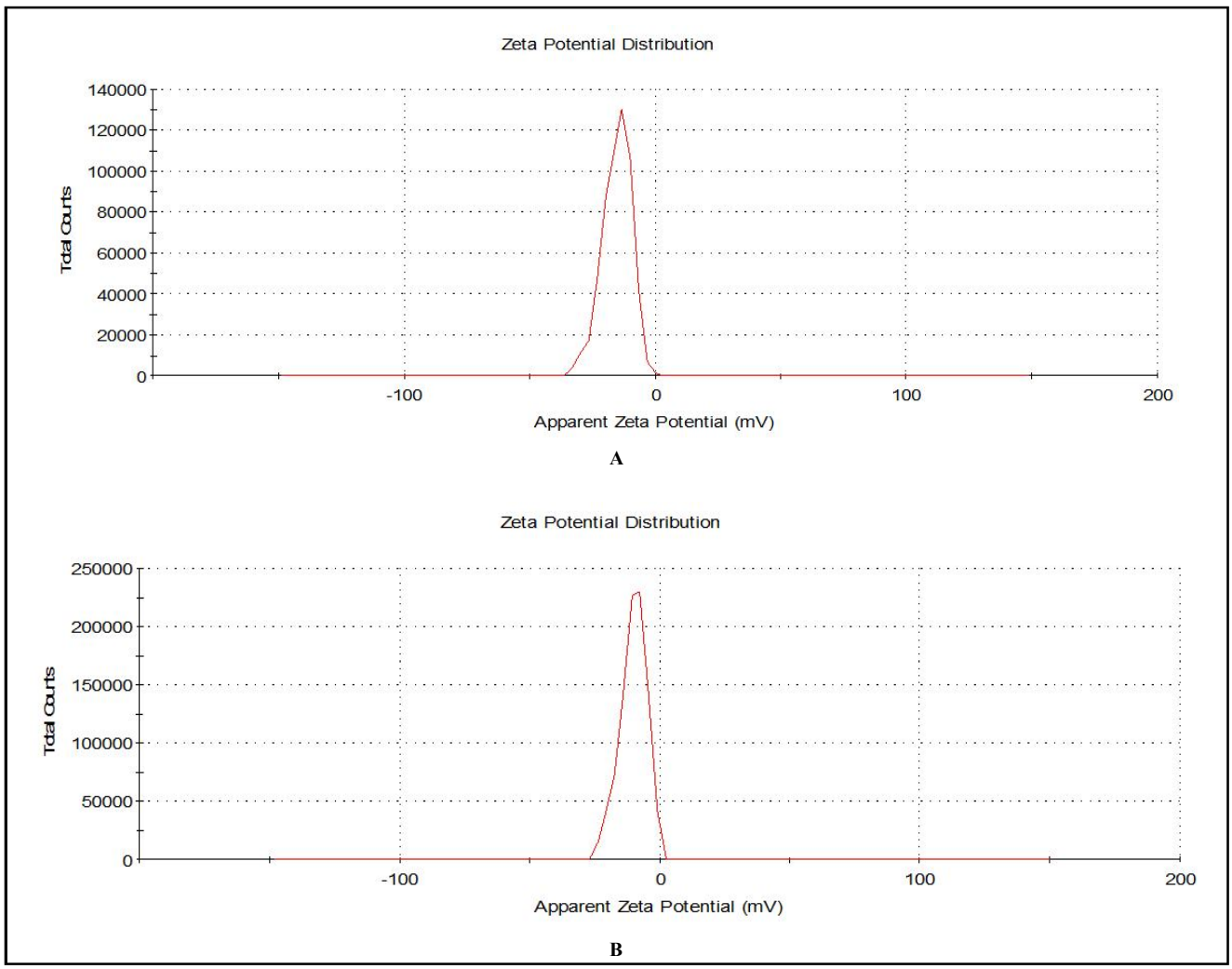


Figure 4: The optimized self-nanoemulsion exhibited a potential of -18.5 mV when unloaded (A) and a potential of -21.16 ± 3.4 mV when loaded with BDQ (B).

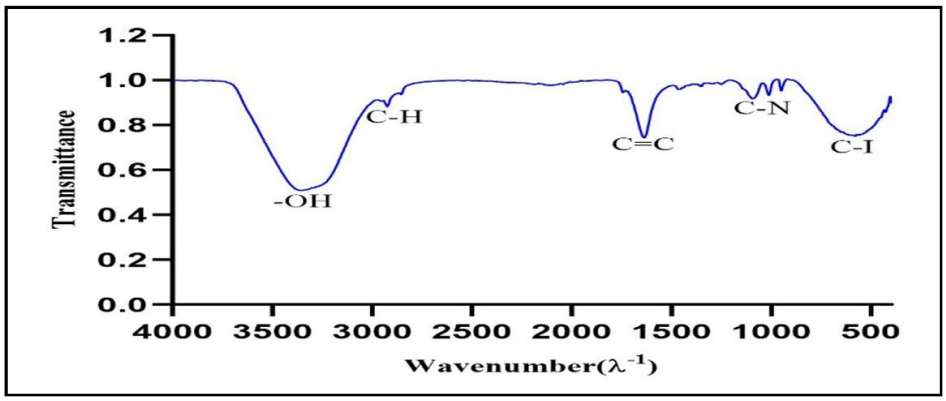


Figure 5: FTIR spectra of bedaquiline SNEDDS.

3.7 Transmission electron microscopy

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are often employed techniques for examining the shape and structure of nanoemulsion droplets. In a transmission electron microscope (TEM), electrons are distributed evenly across the sample to generate the droplet morphology and segregate different chemical constituents based on their densities. The drug-loaded SNNEDS were examined using TEM, revealing particles that were homogeneous, spherical, and smooth in shape. The majority of the particles seen were less than 200nm in size. The transmission electron microscopy (TEM) image visually confirms the presence of droplets that have a spherical form and an average size ranging from 100 to 130 nm, as seen in Figure 6.

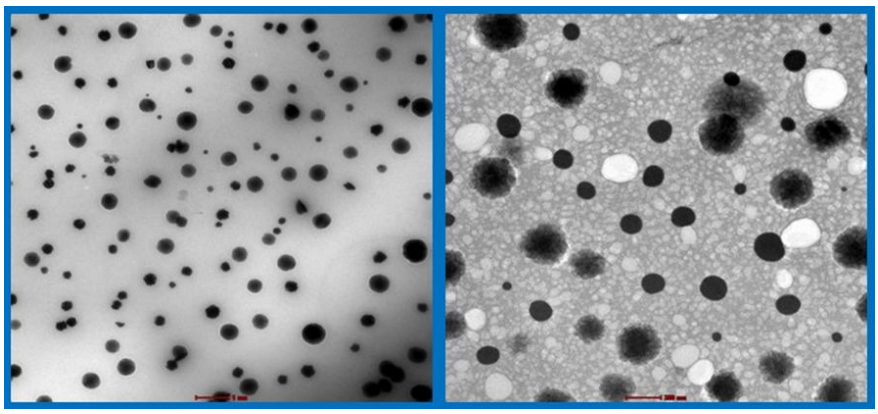


Figure 6: TEM picture provides visual confirmation of spherical-shaped droplets with an average size range of 100-130 nm at different magnification and scale.

3.8 *In vitro* drug release profile

The diagram presented illustrates the proportion of drug released over time for both the optimized BDQ-Pure suspension and BDQ-SNEDDS. During the initial 2 h period, BDQ-SNEDDS exhibited a drug release rate of 34%, whereas the pure solution only released 20% of the medication. BDQ-SNEDDS exhibited a drug release rate of 98% after a 12 h period, which was considerably greater (p<0.05) compared to the 54% release seen from the pure solution (Figure 7). This enhanced release is due to the rapid formation of nanosize droplets, indicating effective solubilization in the formulation's components.

3.9 Antimicrobial activity

To assess the antibacterial activity of BDQ loaded SNEDDS, the agar well diffusion technique was employed (Table 4).

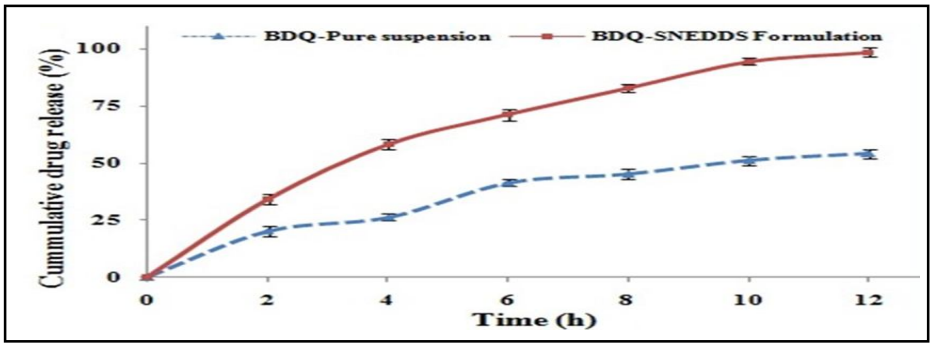


Figure 7: Cumulative drug release (%) from BDQ drug suspension and BDQ-SNEDDS.

Table 4: Antimicrobial activity of optimized bedaquiline SNEDDS against *E. coli* and *P. aeruginosa* using well diffusion method

S. No.	Samples	Drug concentration (mg/ml)	Zone of inhibition (mm)	
			E. coli	*P. aeruginosa*
1.	Placebo control	0	0	0
2.	Drug suspension	2.5	$10.2 \pm 1.5^{*}$	$20.6 \pm 2.8^{*}$
3.	BDQ-SNEDDS (F5)	1.25	$20.5 \pm 2.6^{*,\#}$	$21.4 \pm 1.6^{*,ns}$

All the values were expressed as mean ± SD (n=3). $^{*}p<0.05$ significant when compared with placebo control; $^{\#}p<0.05$ significant when compared with drug suspension; $^{ns}p>0.05$ non-significant when compared with drug suspension.

The inhibition diameter zones obtained by the well diffusion method for *E. coli* and *P. aeruginosa* demonstrated significant antibacterial activity of the BDQ-SNEDDS formulation.

4. Discussion

The clinical application of bedaquiline (BDQ) in treating multidrug-resistant tuberculosis (MDR-TB) is constrained by its poor dissolution and low oral bioavailability. Addressing these limitations, our study focused on developing a self-nanoemulsifying drug delivery system (SNEDDS) to enhance the oral absorption of bedaquiline. The selection of Capryol 90, Cremophor EL, and carbitol as components for the SNEDDS formulation was strategic, based on their superior solubilizing capabilities for bedaquiline. Six different formulations were prepared, optimizing the ratios of these excipients, and distilled water was employed as the aqueous phase. Dynamic light scattering (DLS) analysis played a pivotal role in assessing the particle size of the optimized formulations. The results demonstrated that all six formulations achieved particle sizes below 200 nm after 11 h of stirring followed by sonication. The nanoscale size of the particles is significant for several reasons. Firstly, it enhances the surface area available for dissolution, which is crucial for drugs like bedaquiline that exhibit poor solubility. Increased surface area facilitates a higher dissolution rate in the gastrointestinal tract, leading to improved bioavailability. Furthermore, the zeta potential of the bedaquiline-loaded SNEDDS was measured, revealing a negative value of -21.16 ± 3.4 mV. This negative zeta potential is indicative of good physical stability, as it helps in preventing particle aggregation. A formulation is considered stable and no separation or coagulation is seen, if the zeta potential value is between +30 mV and “30 mV (Rodríguez-Rodríguez *et al.,* 2019). Aggregation can lead to larger particle sizes and instability in the formulation, which can compromise the drug’s bioavailability and efficacy. Therefore, the negative zeta potential observed in our formulations is a promising indicator of the formulation’s stability. Stability studies were conducted on all six formulations, which included tests such as centrifugation and freeze-thaw cycles. Formulation 5 emerged as the most stable among the tested formulations. The stability of SNEDDS is a critical parameter because it ensures the drug remains effective over its shelf life, which is essential for its practical application. The stability observed in formulation 5 can be attributed to the nanoscale particle size and the negative zeta potential, which collectively prevent phase separation and maintain the integrity of the formulation. The potential of SNEDDS to enhance the oral absorption of bedaquiline is significant. Oral bioavailability is a critical factor in the efficacy of drug therapy, especially for conditions like MDR-TB, where consistent and effective drug levels are necessary for treatment success. The enhanced dissolution and stability provided by SNEDDS could lead to better therapeutic outcomes in MDR-TB patients by ensuring higher and more consistent blood levels of bedaquiline. Previous studies indicated that the developed bedaquiline SNEDDS formulation demonstrated favorable cell viability in A549 cells, indicating that the development of bedaquiline SNEDDS is a safer option for oral delivery (Jahan *et al*., 2023). Future studies should focus on *in vivo* evaluation to confirm the enhanced bioavailability observed *in vitro*. Animal studies and subsequent clinical trials will be necessary to establish the pharmacokinetic profile of bedaquiline when delivered *via* SNEDDS. Additionally, the therapeutic efficacy and safety of the SNEDDS formulation should be assessed in these studies to ensure it provides a clear benefit over existing formulations. Moreover, the development of a bedaquiline-loaded SNEDDS offers a promising approach to overcoming the limitations of poor dissolution and low oral bioavailability. By improving these critical parameters, SNEDDS could enhance the therapeutic efficacy of bedaquiline in the treatment of MDR-TB.

5. Conclusion

BDQ-SNEDDS formulations were effectively created and analyzed to overcome the drawbacks of inadequate dissolution. Further study may help to improve absorption and bioavailability of BDQ when administered orally. The results of *in vitro* drug release experiments showed that the improved BDQ-SNEDDS released greater levels of bedaquiline (98%) compared to its suspension (54%) during 12 h. This indicates that the improved BDQ-SNEDDS formulation efficiently releases the medication in elevated amounts. The optimized formulation exhibited increased stability and greater antibacterial efficacy as there was no significant change observed in droplet size, zeta potential and other parameters after 30 days of storage. The current study suggests that BDQ-SNEDDS formulations have potential for further investigation in the treatment of multidrug-resistant TB.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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