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Development and Evaluation of Berberine-Loaded Self-Nanoemulsifying Drug Delivery System (SNEDDS) for the Treatment of Acne Vulgaris

Aja Alam*[1], Ran Vijay Singh[2], Dr. Sanjay Kumar Kushwaha[3]

[1]Research scholar, [2]Associate Professor, [3]Professor, Bhavdiya Institute Of Pharmaceutical Sciences And Research, Faizabad, U.P., INDIA

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ABSTRACT

The objective of this study was to design a successful self-nanoemulsifying drug delivery system (SNEDDS) for berberine to improve its solubility, dissolution rate, and treatment of acne. According to solubility and emulsification studies, oleic acid, tween 20, and glycerol were selected as system excipients. A pseudo ternary phase diagram was constructed to reveal the self-emulsification area. The developed SNEDDS were visually assessed, and the droplet size was measured. In vitro release studies and stability studies were conducted. The antimicrobial effectiveness against multiple bacterial strains, including Staphylococcus aureus, methicillin-resistant Staphylococcus aureus (MRSA), and different accessory gene regulator (Agr) variants were investigated. Characterization studies showed emulsion homogeneity and stability with low droplet sizes. It was found that the developed BER-SNEDDS provided significantly a higher release rate (>96 % in 1 h) as compared to the raw drug (<10 % in 1 h). The in vitro antimicrobial activities of pure BER and BER -loaded SNEDDS demonstrated a remarkable inhibitory effect on bacterial growth. These outcomes suggested that SNEDDS could be a potential approach for improving solubility, dissolution rates, and antiacne activity of BER.

Keywords: BERBERINE, SNEDDS (self-nanoemulsifying system), In vitro dissolution, acne

INTRODUCTION

Adolescents are 70–85% likely to have acne, a common cutaneous condition (1). Propionibacterium acnes causes inflammation beneath hair follicles, keratinisation alterations, and sebum production. Furthermore, Staphylococcus aureus has a role in opportunistic infections that lead to atopic dermatitis or acne (2). As a result, acne is a chronic condition that can lead to unpleasant physical and emotional consequences, including lifelong scarring lesions, anxiety, social sadness, and suicide thoughts (3). Benzoyl peroxide, topical antibiotics (clindamycin and erythromycin), and topical retinoids (tretinoin, isotretinoin, retinaldehyde, and retinol β-glucuronide) are the most often prescribed medications for acne (4).

Additionally, photodynamic therapy and radioactive decontamination have been accomplished with nanoemulsions. Nanoemulsions have been effectively used as innovative nanocarriers for topical applications in the formulation of several therapeutic agents, including lipid medications, antioxidants, and nonsteroidal anti-inflammatory medicines. As a result, nanoemulsions have advanced in the field of dermatology (5). Self-nanoemulsifying drug delivery systems, or SNEDDS, have grown in importance and prominence within the pharmaceutical industry in recent years. The systems have been shown to be effective nanocarriers for increasing the bioavailability of medications that are poorly soluble, particularly topical medications. A medication, oil, a surfactant, and a cosurfactant make up SNEDDS, which are isotropic mixes (6). By enhancing drug release and membrane permeability and decreasing efflux pumps presystemic metabolism, SNEDDS advantageously offer the drug in a dissolved state and their comparatively tiny droplet size provides a wide interfacial surface, which increases drug absorption and bioavailability. (7) However, SNEDDS topical treatment may have a number of disadvantages, including the possibility of producing allergic contact dermatitis, reducing penetration in the diseased region, and perhaps changing the cutaneous flora (8).

One of the main ingredients of Coptis chinensis Franch is berberine. Due of its substantial impact, it has been used in therapeutic settings for many years. Additionally, berberine, a lipophilic antibacterial agent (9), has anticancer (12), antidiarrhea (11) and hypoglycemic (10) qualities. Tablets and capsules are now the dosage forms that are commercially offered. Because of the drug's poor solubility, both of these have low and inconsistent oral bioavailability. The current study was developed to create an optimized SNEDDS formulation of berberine using pharmaceutically acceptable, non-toxic, and safe substances to improve its poor bioavailability and antimicrobial activity.

MATERIALS AND METHODS

Materials: berberine (purity > 99.5 %) was obtained by yarrow chem pvt ltd, mumbia. Tween® 80, Tween® 20, castor oil and turpentine oil were obtained from Sigma–Aldrich (St. Louis, MO, USA). Propylene glycol (propane-1, 2-diol) was obtained from Winlab (Gemini-house, England). Cremophor EL was supplied from S.D Fine Chemicals.

Screening of components

Solubility analysis: Excess berberine was added to 2 millilitres of oils, surfactants, and co-surfactants (such as rice bran oil, oleic acid, almond oil, soybean oil, peppermint oil, Tween 40, Tween 80, Span 20, PPG, PEG 400, PEG 600, and glycerol) in order to determine the equilibrium solubility. Each sample was vortexed for 48 hours at 40 °C in a shaking water bath to aid in solubilisation. After that, the mixture was centrifuged for 30 minutes at 5000 rpm. Following centrifugation, the supernatant was collected, combined with methanol to dilute it, and then subjected to spectrophotometric analysis using a UV visible spectrophotometer at λmax 346 nm. (13)

Surfactant and co-surfactant screening study: Berberine's solubility and emulsification were assessed in a range of co-surfactant (PEG 600, PEG 400, PEG 200, PPG, and glycerol) and surfactant blends (Tween 80, Span 20, Tween 20, and Span 80). Then, 5 ml of each selected oil component (oleic acid) was mixed with 5 ml of surfactant and co-surfactant separately. The mixture was then gradually heated to 40–65 °C to ensure that all of the components were completely homogenised. Two millilitres of this isotropic mixture were precisely transferred to ten millilitres of distilled water and diluted. The turbidity of the resulting emulsion was examined visually. (14, 15)

Preparation of SNEDDS: The ternary phase diagram's self-emulsifying area was used to choose various ratios of oil, surfactant, and cosurfactant to create the SNEDDS formulations. Table 3 displays the four batches that were created. In a screw-capped glass vial, 30 mg of the medication was first added to precisely weighed amounts of oil and cosurfactant. After achieving homogeneity by vortexing, the liquid was heated to 50 °C until it turned clear. To create the final SNEDDS combination, the weighed quantity of the surfactant was then added to the preconcentrate while being vortexed. For later usage, the formulations were kept at room temperature. (16)

Pseudo-ternary phase diagram: The ternary phase diagram, the oily phase (oleic oil), the surfactant phase (Tween 20), and the cosurfactant phase (glycerol) were constructed using specific components. Depending on the process, they were combined in various ratios. At 37 ± 0.5 ◦C, one gramme of each product was diluted 200 times with distilled water and was agitated at 100 rpm. To assess the spontaneous nanoemulsion generation, visual observation was done. After verifying clarity by measuring the transmittance percentage (% T), the emulsions were ranked based on their transparency percentage, as indicated in Table 3. Only emulsions classified as clear (A-grade) or translucent (B-grade) were taken into consideration for the phase diagram. (17, 18)

Physicochemical Evaluation Of BER-Loaded SNEDDS: The developed BER-loaded SNEDDS (BF1-BF9) were evaluated for various physico-chemical parameters, such as percentage of transmittance (%T), droplet size (PS), polydispersity index (PDI), percentage of content, in vitro release and thermodynamic stability.

Visual assessment method: The primary method for evaluating the formulations' self-emulsification effectiveness was visual inspection. At 37 ± 0.5 ◦C, 1 ml of each SNEDDS formulation was diluted with 200 ml of distilled water and continuously swirled at 100 rpm. The compositions' appearance, clarity, and miscibility were assessed visually. Using deionised water as a blank, the transmittance % was determined spectrophotometrically at 346 nm. It was noted how long it took for the emulsion droplets to vanish and form a fine emulsion. (17)

Droplet size (PS) and polydispersity index (PDI): When evaluating an emulsion's effectiveness in terms of physical stability, drug release rate, and extent, droplet size is an important consideration. Another crucial component for demonstrating the homogeneity of the size distribution is the polydispersity index (PDI). The Malvern Zetasizer (Model ZEN3600, Malvern, UK) was used to assess the droplet size and polydispersity index (PDI) of the chosen SNEDDS formulations using a laser light diffraction analysis approach. Distilled water was added to the formulations at a 1:1000 v/v ratio while stirring for one minute. Samples were then put into cuvettes, and each sample had 10 readings taken. (18)

Percentage of content: BER-loaded SNEDDS formulations with 10 mg of medicine each were tested for drug content. In conclusion, 0.1 g of each sample was diluted with 25 ml of methanol, vortexed, and then analysed at 346 nm using a UV spectrophotometer. For comparison, methanol was used as a reference solution blank. The standard calibration curves that were previously made for the drug in methanol were used to determine the quantity of the drug. (19)

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In vitro release studies: The United States Pharmacopoeia (USP) dissolving apparatus type II (model: ERWEKA dissolution rate testing device DT 600, Heusenstamm) was used to examine the in vitro release of BER from the chosen SNEDDS formulations in accordance with FDA guidelines. One gramme of formula, or 10 mg of BER, was used for the dissolving, and the paddle stirrer speed was set at 75 rpm. The test was run for one hour at 737 ± 0.5 ◦C in 900 cc of 0.05 M phosphate buffer (pH = 7.8). At specified intervals of 5, 10, 15, 30, 45, and 60 minutes, samples were taken out, filtered through a 0.45 µm syringe filter, replenished with new buffer, and subjected to UV analysis at 346 nm. Every experiment was conducted three times. (20)

Thermodynamic stability: By putting formulations through three phases of stress—heating and cooling, centrifugation, and freeze-thaw cycles—the kinetic stability of the produced nanosized emulsions was examined. The first test phase included three heating-cooling cycles that lasted 48 hours at each temperature for storage, ranging from 4 °C (refrigerator) to 50 °C (oven). Following their satisfactory completion of the first testing phase, the formulations were subjected to the second examination. The formulations were centrifuged for 30 minutes at a temperature of 25 °C and 3500 revolutions per minute (rpm) throughout this phase. Formulations evaluation, which involved subjecting the formulations to three freeze/thaw cycles, with temperatures ranging from -21C◦ (freeze) to + 25 ◦C (thaw), for a minimum duration of 48 h. (21)

In vitro antimicrobial activity of pure BER and BER-loaded SNEDDS: As indicated in Table 5, five distinct strains of Staphylococcus aureus—including methicillin-resistant Staphylococcus aureus—were employed in this investigation. The control organism was Staphylococcus aureus bacterium. (22)

Culture and media conditions: MRSA (methicillin-resistant Staphylococcus aureus), wild-type Staphylococcus aureus, and several QS mutants (Agr1, Agr2, and Agr3) were cultivated in tryptic soy broth (TSB) and incubated for 18 to 24 hours at 37 °C. After adjusting the solutions to the 0.5 McFarland standard, they were shaken continuously at 200 rpm for the whole night. (22)

Determination of the antibacterial inhibition zone: Inhibition zone monitoring was used to assess the optimised SNEDDS formulation's (BF5) in vitro antibacterial efficacy. A volume of the bacterial suspension was applied to the whole surface of the agar plate in order to inoculate it. After using a sterile cork borer to aseptically punch a hole of 6 to 8 mm in diameter, 100 µL of the produced berberine-loaded SNEDDS was added to the well at varying doses (2.5, 5, and 10 mg/ml) in comparison to the pure drug solution. For 18 hours, agar plates were incubated at 37 °C, depending on the test microbe. Inhibiting the development of the tested microbiological strain, the antimicrobial drug diffuses throughout the agar medium. (23)

Determination of minimum inhibitory concentration (MIC):): Using the broth dilution technique and the bio screen C system (Growth Curves USA, Piscataway, NJ, USA), the minimum inhibitory doses (MICs) of pure BER and BER loaded SNEDDS were ascertained. This technique measured a solution's turbidity, which represented the growth of bacteria at various doses of the additional antimicrobial ingredient. (23)

RESULTS AND DISCUSSION

Solubility of drug in oils, surfactants and co- surfactants: The right excipients, such as oil, surfactant, and co-surfactant, must be chosen in order to produce a transparent and monophasic self-emulsifying nanoemulsion. Excipients that exhibit the highest solubility and yield stable formulations were chosen. Solubility in different excipients is regarded by the SNEDDS method as a crucial requirement. The medication decreased the interfacial barrier and provided a mechanical barrier to coalescence. It was soluble in the oil phase and in the surfactants and co-surfactants of the self-micro emulsifying system. Selecting an oil with higher solubility is crucial to preventing medication precipitation during dilution.

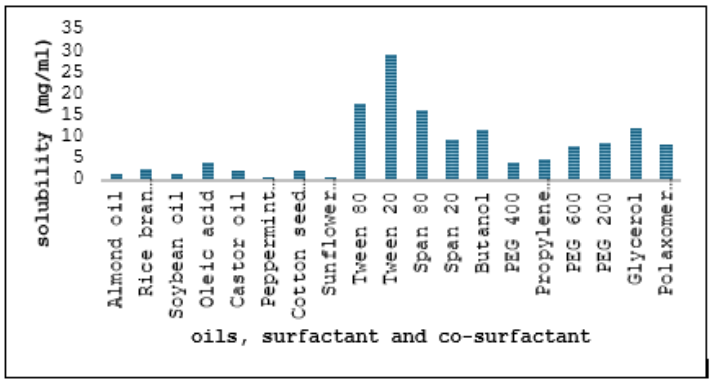

Figure 1: Solubility of berberine in different oils, surfactants and co-surfactants

The drug's solubility measurement values in different oils, surfactants, and co-surfactants are shown in Figure 1. It establishes how soluble berberine is in various oils, surfactants, and co-surfactants. Because of their maximum solubility among the other excipients, the oils chosen from the solubility studies—oleic acid as the oil phase, Tween 20 as the surfactant, and glycerol as the co-surfactant—were chosen.

Surfactant and co-surfactant Screening investigation

Screening of surfactants and co-surfactant for emulsifying ability with oleic acid: The result of emulsification efficiency of surfactants and co-surfactants are given in Table 1.

Table 1: Emulsification efficacy of surfactant and co-surfactant with oleic acid

S. No.	Surfactants and co-surfactants used	Emulsification
1	Span 80	Phase separation
2	Tween 80	Emulsifies
3	Tween 20	Emulsifies
4	Span 20	Emulsifies
5	PEG 400	Emulsifies
6	PEG 600	Emulsifies
7	PEG 200	Phase separation
8	Glycerol	Emulsifies

Based on the data above, it was determined that the co-surfactants PEG 400, PEG 600, and PPG, as well as the surfactants Tween 80, Tween 40, and Span 20, had an excellent capacity to emulsify with oleic acid. Berberine is most soluble in the surfactant (Tween 20) and co-surfactant (Glycerol), per the results of solubility screening research. Thus, oleic acid was selected as the oil and Tween 20 and glycerol as the surfactant and co-surfactant, respectively.

Preparation of SNEDDS: After the selection of oleic acid as oil phase, surfactant as Tween 20 and Glycerol as co-surfactant, SNEDDS formulations were prepared as shown in table 2. All the formulations did not show phase separation and appearance of turbidity after 24 h.

Table 2: Preparation of SNEDDS using oleic acid, Tween 20 and Glycerol

S. No.	Code	SCO Smix(ml)			Berberine (mg)
1	BF1(9:1)	1:1	1:2	2:1	30
2	BF2(8:2)	1:1	1:2	2:1	30
3	BF3(7:3)	1:1	1:2	2:1	30
4	BF4(6:4)	1:1	1:2	2:1	30
5	BF5(5:5)	1:1	1:2	2:1	30
6	BF6(4:6)	1:1	1:2	2:1	30
7	BF7(3:7)	1:1	1:2	2:1	30
8	BF8(2:8)	1:1	1:2	2:1	30
9	BF9(1:9)	1:1	1:2	2:1	30

Data expressed as Mean ± SD, n= 3.

Construction of pseudo ternary phase diagram: The surfactant and co-surfactant weight ratios of 1:1, 1:2, and 2:1 were varied to obtain this figure. Figures 3.7, 3.8, and 3.9 display the self-emulsifying region (brown area) at each SCOSmix ratio. Tables 3.7, 3.8, and 3.9 display the composition of oleic acid, Tween 20, glycerol, and water for each Km value. Km values indicate the mass ratio of the surfactant to the co-surfactant for the creation of the self-emulsifying zone in a pseudoternary phase diagram.

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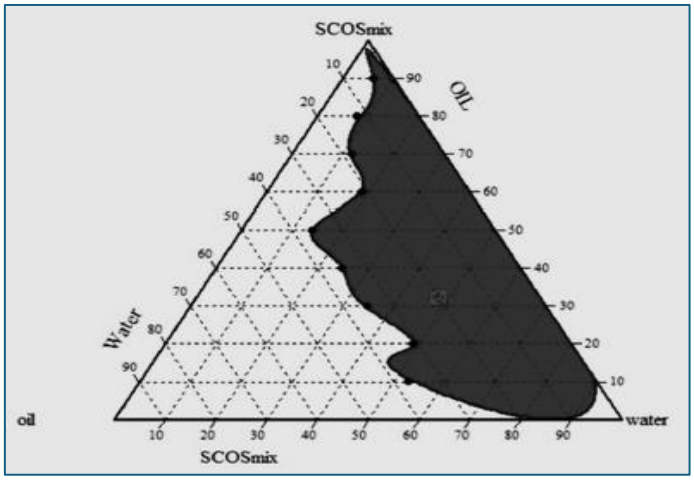

Figure 2: Ternary phase diagram of oleic acid, Tween 20, Glycerol and water at SCOSmix ratio 1:1.

The resulting dispersion's characteristics, including phase separation, coarse emulsion, and emulsification region, are provided by the pseudoternary phase diagram. Because of its larger self-emulsifying zone, the 1:1 weight ratio of SCOSmix was determined to be the best of the three. Higher self-emulsifying regions, which correlate to higher water absorption capacities, were the basis for the selection. It was demonstrated that the emulsifying area in both oils is increased when surfactant and cosurfactant are mixed in the same ratio. The observation led to the decision to create and characterise a number of SNEDDS containing berberine for various assessment studies.

PHYSICOCHEMICAL EVALUATION OF BER-LOADED SNEDDS

Visual assessment and self-emulsification: The four emulsions (BF1-BF9) produced fine bluish/transparent (A-graded) systems with no visible particulates, demonstrating the ability of the used surfactant to promote self-emulsification at oil contents of 10%–20% (w/w). Visual evaluation of the four SNEDDS formulations verified emulsion homogeneity and miscibility. The measured transmittance percentage, which was close to 100%, verified clarity. The studied formulations' emulsification times varied from 10 to 40 seconds. It was found that formulations with a low oil content of 10–20% w/w and a high cosurfactant content of 50–70% w/w that result in mixes with low viscosities were aided by quick emulsification. The SNEDDS (BF1-BF9) transmittance percentage ranged from 93.11 ± 2.85% to 98.76 ± 4.11 %, indicating a nanometric droplet size with a wide surface area for drug release and improved bioavailability.

Droplet size (PS) and polydispersity index (PDI) measurement: It was discovered that the diluted SNEDDS formulations had mean droplet sizes that were within the nano size range (<200 nm). When diluted with water, the formulation with the highest cosurfactant concentration and the least amount of oil generated droplets with the smallest size (BF1, 31.87 ± 23). Nevertheless, when the oil content rose, so did the droplet diameters. The formulation BF3, which had a mean droplet size of 115.47 ± 0.36 nm, included 30% w/w oil. In contrast, droplets from formulations BF2 and BF4 had low polydispersity values of 0.22 and below, suggesting high size distribution homogeneity.

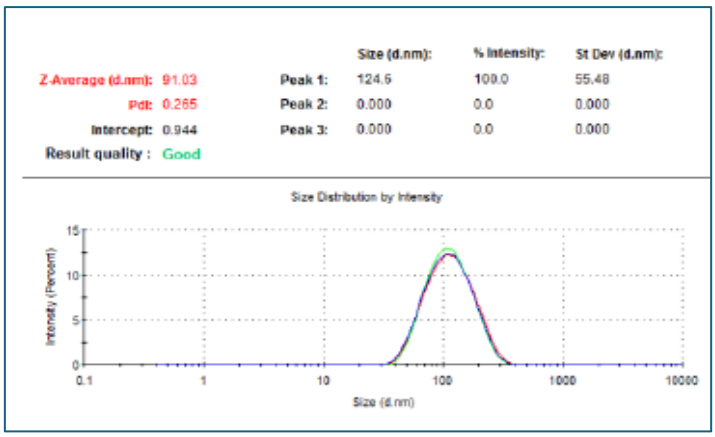

Figure 3: Droplet size (PS) of formulation BF5

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Zeta potential: The potential between the droplets' surface and the dispersion medium is known as the zeta potential. It is a measure of the formulation's stability; a value greater than +30 mV and less than -30 mV indicates a stable formulation that is resistant to coalescence and separation. By measuring the droplets' electrophoretic mobility, its value is calculated. There was no coagulation, flocculation, or agglomeration in the formulation, and the zeta potential of BF5-SNEDDs was determined to be −13.5 ± 0.87 mV.

Percentage of drug content determination: The drug content of the four tested SNEDDS formulations was calculated using the calibration curve of BER prepared in methanol. Despite the difference in formulation compositions, the essays for drug content among the formulations (BF1-BF9) were found to be in the range of 98.51 % and 101.27 %. This complies with the USP guidelines acceptance range (±5 %).

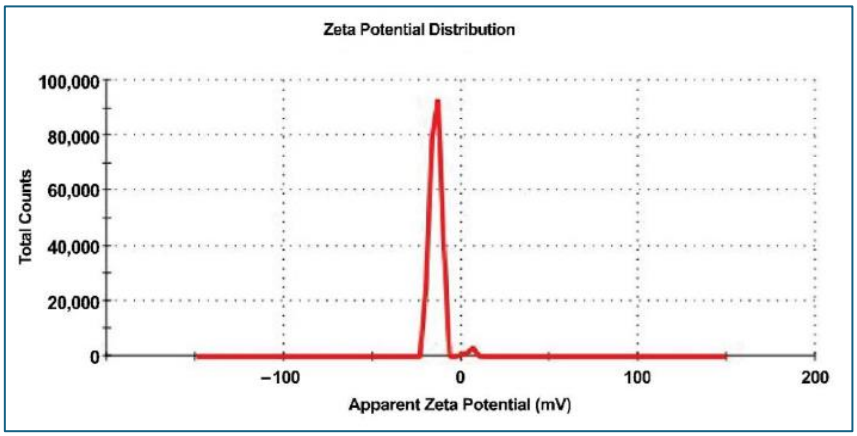

Figure 3.11: Zeta potential of formulation BF5

Table 3: Emulsification time and % drug content

Formulation No.	Emulsification Time (sec)	Drug Content (%)
BF1	10.64	98.51
BF2	19.64	95.64
BF3	38.99	101.27
BF4	23.64	98.65
BF5	32.55	101.34
BF6	33.75	95.53
BF7	42.38	93.67
BF8	26.64	99.66
BF9	16.40	99.38

In vitro release study: In vitro release patterns of plain BER and the tested SNEDDS formulations (BF5 and BF9) in a 0.2 M phosphate buffer (pH = 7.8) were displayed in Fig. 4. In order to track the occurrence of precipitation over time, BER only showed a 10% release within ten minutes due to its insoluble nature. The four liquid SNEDDS formulations demonstrated BER release of over 50% within 4 hours and over 80% within 30 minutes.

With the greatest cumulative percentage of release of 97% after five minutes, BF5 had the best release behaviour out of the four SNEDDS formulations. As a result, all SNEDDS formulations' dissolving patterns guaranteed a notable rise in BER release ($p < 0.05$). According to the findings of the total dissolving trial, the BF5 formulation had a BER release that was much greater than that of the raw drug powder and the other comparable formulations. The BF5 formulation was thus chosen for additional microbiological research.

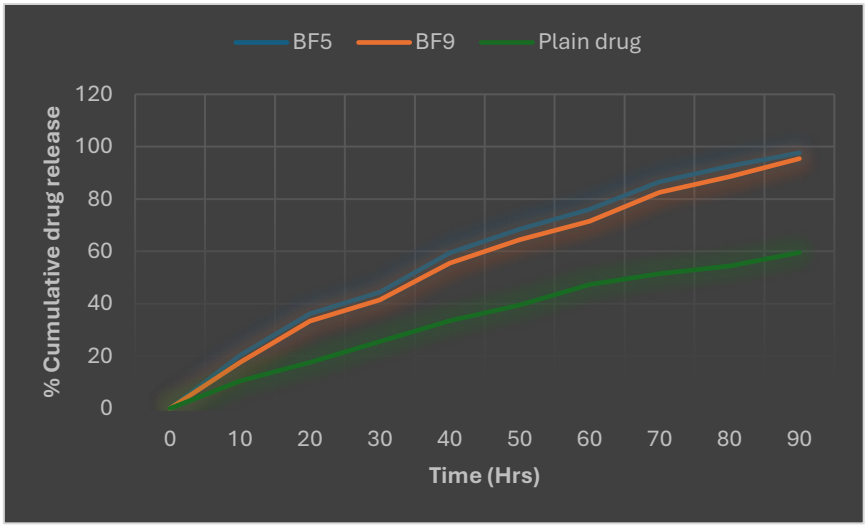

Figure 4: In-vitro drug release

Thermodynamic stability study: The formulation's stability was significantly influenced by the amount of oil it included. Formulations containing 10–20% oil were found to be able to pass the stability study (BF1–BF7), whereas formulations using 30% oil (BF8 and BF9) were unable to do so because of phase separation and drug precipitation.

In vitro antimicrobial activity & determination of inhibition zone: When compared to pure BER, the BER-loaded SNEDDS formulation showed a stronger antibacterial action, with a greater inhibitory impact at a dosage of 5 mg/ml. Additionally, the MIC analysis showed that BER and SNEDDS had comparable inhibitory effects on SA and MRSA, with both having a MIC of 5 mg/ml. However, BER showed a MIC of 5 mg/ml when analysing the Agr variations (Agr 1, 2, and 3). In contrast, SNEDDS showed a lower MIC of 2.5 mg/ml, highlighting the formulation's enhanced antimicrobial effectiveness against Agrregulated bacterial isolates.

All bacterial strains showed notable changes between SNEDDS and BER treatments, according to statistical analysis of optical density data. These findings imply that the SNEDDS formulation increases BER's antibacterial activity, which might lead to better treatment outcomes for bacterial infections.

Table 4: MIC (mg/ml) Values of Pure BER and SNEDDS against Various Bacterial Isolates.

Bacterial isolates S. aureus	BER ITN (5 mg/ml)	BER-loaded SNEDDS (5 mg/ml)
MRSA	5 mg/ml	5 mg/ml
Agr 1	5 mg/ml	2.5 mg/ml
Agr 2	5 mg/ml	2.5 mg/ml
Agr 3	5 mg/ml	2.5 mg/ml

CONCLUSION

This work successfully developed a self-nanoemulsifying medication delivery device for berberine. It may be possible to use this delivery method to increase a drug's antibacterial effectiveness. Other solid self-nanoemulsifying drug delivery devices may be developed using the same process. The BER-SNEDDS formulations effectively addressed berberine's low bioavailability by increasing its solubility and rate of dissolution. The formulations showed promise in treating bacterial infections by exhibiting strong antimicrobial activity against a range of bacterial strains, including those resistant to antibiotics.

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