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Development, Characterization, and *In-vitro* Evaluation of Self-nanoemulsifying Drug Delivery System for Ofloxacin

Hafiz Hanzla Irfan^{1*}, Nader I. Namazi², Saba Nazeer¹, Shafiullah^{1*}¹ Department of Pharmaceutical Sciences, Faculty of Pharmacy, Superior University, Lahore, Pakistan.² Department of Pharmaceutics and Pharmaceutical Industries, Taibah University, Saudi Arabia.

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ABSTRACT

Ofloxacin (OFX), a fluoroquinolone characterized by poor solubility and extensive distribution, demonstrates minimal oral absorption. This research aimed to develop *OFX* self nanoemulsifying drug delivery system (*SNEDDS*) to increase its solubility. Different oils, surfactants, and co-surfactants were tested to select ones having maximum solubility of the drug. The selected oils, surfactants and co-surfactants were mixed in different ratios to obtain optimized pre-concentrated and characterized using a *Zeta-sizer* and *FTIR*. This study investigates the *in vitro* properties of *Ofloxacin-SNEDDS* to enhance solubility, absorption, and therapeutic efficacy, thereby reducing the frequency of dosages and associated side effects. In the *OFXPO2* formulation, particle size of 141.78 ± 4.25 , polydispersity index (PDI) 0.236 ± 0.007 , and zeta potential of -17.9 ± 0.54 were observed. Compared to the reference formulation, the *OFXPO2* formulation exhibited improved dissolution and antimicrobial activity. The study indicates that *SNEDDS* made of the selected ingredients can increase solubility and therapeutic activity of ofloxacin.

Keywords: *Ofloxacin, Self-emulsification, Poor water solubility, Zeta Potential.*

Corresponding Authors: Hafiz Hanzla Irfan

Email: hanzlairfan7@gmail.com

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INTRODUCTION

Ofloxacin is a fluoroquinolone that demonstrates broad-spectrum antibacterial activity (Figure 1). It is effective against both actively dividing and dormant bacteria by inhibiting bacterial DNA gyrase. Ofloxacin can be used to treat a variety of systemic and local infections. Its half-life is approximately 6-7 hours. The drug is minimally soluble in water and methanol and is classified as a BCS class II drug, meaning it has low solubility but high permeability (Jagdale and Pawar, 2017). The administration of ofloxacin is appropriate for urinary tract infections, dermatological conditions, prostatitis, and lower respiratory infections caused by susceptible bacterial species. This antibiotic is effective in treating both *acute gonococcal infections* and *nongonococcal urethritis* resultant from *Chlamydia*, as well

as *cervicitis*. Due to its limited efficacy against most anaerobic bacteria, the medication should not be utilized as a sole treatment option in the context of mixed aerobic-anaerobic bacterial infections. Patients are advised to take a maximum oral dosage of 400 mg of ofloxacin daily in the morning, with the possibility of increased dosing of 400 mg administered twice per day. Administering a 0.2% solution requires a 30-minute infusion, while the 0.4% solution requires a 60-minute infusion. The uptake of ofloxacin occurs promptly and efficiently; consequently, its intravenous formulation does not confer enhanced efficacy or augmented antimicrobial activity compared to oral administration (Al-Omar, 2009).

Numerous studies have investigated strategies to enhance solubility. Typically, a drug has low solubility in water or

dissolves solely in organic solvents. Based on the Noyes-Whitney equation, reducing particle size speeds up the dissolution of poorly water-soluble drugs, a technique that has been thoroughly researched for more than thirty years. SNEDDS can significantly enhance the surface area of pharmaceuticals. In instances where drugs exhibit exceptionally low water solubility, merely augmenting their surface area may prove insufficient to improve bioavailability when administered orally. To overcome this

limitation, a prominent approach involves further diminution of globule size via a process known as nanosization. Unlike micronized medications, SNEDDS are specifically formulated to augment saturation solubility in addition to increasing surface area. The production of SNEDDS is anticipated to enhance the drug dissolution rate by simultaneously increasing saturation solubility and reducing globule size, thereby increasing the surface area (Merisko-Liversidge and Liversidge, 2008).

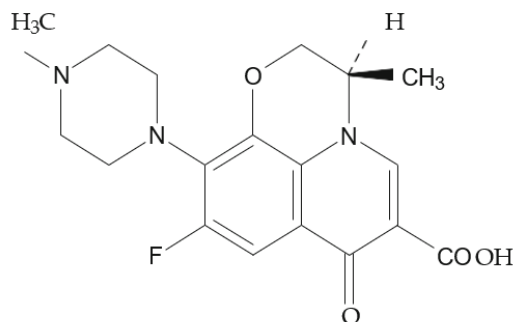


Figure 1: Chemical Structure of Ofloxacin (Al-Omar, 2009).

Nanotechnology is utilized to improve water solubility, enable targeted delivery to specific tissues and cells, facilitate the translocation of pharmaceuticals across tight epithelial and endothelial barriers, and support combination delivery in therapeutic regimens. When considering the relationship between a drug's size and its surface area, a smaller drug size corresponds to a larger surface area (Wanigasekara and Witharana, 2016). A greater extent of the drug's dispersion results in a more rapid release within the gastrointestinal tract. The particle size was decreased to augment its surface area, thereby enhancing its oral bioavailability (Yu, 1999).

The development of new pharmaceuticals is a lengthy process, generally taking between 15 and 20 years (Adams and Brantner, 2006; Domingos et al., 2015). Enhancing the current API's efficacy is a compelling strategy. The estimated costs for new drug development during the years 1989 to 2002 are projected to range from \$562 million to \$2623 billion, covering both preclinical and clinical expenses (Adams and Brantner, 2006). Considering the extended duration and significant costs involved, we mustn't delay in providing prompt treatment for diseases that necessitate immediate intervention (Adams and Brantner, 2006). The phrase 'the silent pandemic'—referring to antibiotic resistance—has become increasingly common in publications, political speeches, and social media (Mendelson et al., 2022). The proliferation of antibiotic resistance is

increasing, thereby complicating the process for patients to obtain the necessary medications and resulting in elevated rates of illness and mortality (23). Consequently, an increase in complex cases requiring extended treatment durations is observed, often resulting in prolonged hospitalizations. When antibiotics fail to eradicate a particular bacterium, all of its progeny will similarly exhibit resistance to the medication unless new mutations arise beforehand. The SNEDDS is an isotropic blend of oils, surfactants, co-surfactants, and the active pharmaceutical ingredient. It features globules smaller than 200 nm (Gursoy and Benita, 2004). The selection of surfactants was a critical step, as it may induce specific biological effects, such as gastrointestinal responses. The physical and chemical compatibilities with all components were comprehensively evaluated (Gursoy and Benita, 2004). Using SNEDDS to enhance the absorption of drugs that dissolve slowly in lipids can lead to improved efficiency, greater reliability, and a more stable concentration-time profile. It is hypothesized that SNEDDS aid in reducing the variability of bioavailability across individuals, as this formulation exhibits lower susceptibility to variables such as the drug's solubility in gastric fluids and the person's dietary habits (Balakumar et al., 2013).

MATERIALS AND METHODS

Materials

Don Valley Pharmaceuticals, Lahore, Pakistan, generously

supplied Ofloxacin. Almond Oil was procured from HJOPC Pakistan. Peppermint oil and Arachis oil were obtained from Nauman Oil Company. Olive oil was acquired from Pasolivo. The oleic acid sample was sourced from Pak Chemical Company. Tween-20 and Tween-80 were obtained from Islam Pharmaceuticals in Sialkot, Pakistan. Polyethylene Glycol (PEG) was obtained from Ishtar Company. Polyethylene Glycol (PEG-400) was acquired from BASF Pharma. Only reagent-grade chemicals were utilized.

Components Of SNEDDs

Oil

We tested Ofloxacin's solubility in different oils. A sufficient amount of Ofloxacin was mixed with 2 mL of each oil and stirred with a magnetic stirrer at room temperature for 24 hours to achieve maximum solubility. Afterward, each mixture was centrifuged for 10 minutes at 6000 rpm. The supernatant was collected, then diluted with methanol, and was filtered through a 0.45 μm membrane filter (Whatman, Maidstone, UK). The drug concentration was measured using a UV-spectrophotometer with methanol as the blank at a wavelength of 314.5 nm (Pawar et al., 2025).

Surfactants

Surfactants, specifically Tween 80 and Tween 20, were selected to evaluate the emulsification capacity of the designated oil phase. A total of 300 mg of surfactant was combined with 300 mg of the chosen oils. The mixtures were then carefully warmed and diluted by transferring 50 mg of each into 50 mL of distilled water in a corked conical flask. The number of flask inversions needed to create a uniform emulsion was documented to evaluate how easily emulsification occurs. Afterwards, the emulsions were left undisturbed for 2 hours. After this period, transparency was measured at 638 nm with a UV-visible spectrophotometer, using distilled water as the blank. Three readings were taken for each sample to determine the average. The emulsions were also visually assessed for turbidity or phase separation (Al-Omar, 2009; Mohite et al., 2024).

Co-surfactants

Co-surfactants were chosen for developing SNEDDS based

on their transparency percentage at 638 nm, measured through UV spectrophotometry, and their emulsification ability. The emulsification test involved mixing 100 mg of each co-surfactant with 200 mg of the designated surfactant and 300 mg of the chosen oil (Asghar et al., 2022; Date and Nagarsenker, 2007).

Preparation of Pseudoternary phase diagram (PTPD)

Following the analysis of emulsification and solubility studies, we selected Peppermint oil, Tween-80, and PEG 400 for subsequent investigation. The concentrations of each component were then measured, and a PTPD was created using the water titration method. Tween-80 and PEG 400 were mixed in various ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1). Oil and S_{mix} (Surfactant/Co-surfactant) were combined in different ratios (10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, 90:10). The proportions of each component were analyzed using a pseudo-ternary plot. The PTPD was developed with CHEMIX® software, testing various oils, surfactants, and co-surfactants (Okonogi et al., 2021). The phase diagram was created by measuring the total water requirement of the emulsion as a weight-to-weight (w/w) ratio. This data was then used with a phase diagram software to determine the nanoemulsifying zone and construct the phase diagram. All experiments were performed in triplicate, yielding consistent results (Asghar et al., 2022; Beg et al., 2012).

Preparation of SNEDDS

An accurate quantity of OFX and excipients was precisely weighed (Wei et al., 2005). The OFX was dissolved in surfactants by placing it in a water bath at 60°C with continuous shaking. After it was fully dissolved, extra excipients were added, and the mixture was then cooled. OFXAO1 to OFXAO3 are SNEDDS formulations of OFX combined with almond oil. OFXPO1 to OFXPO3 are SNEDDS of OFX with peppermint oil. OFXAR1 to OFXAR3 are SNEDDS of OFX with arachis oil. OFXOL1 to OFXOL3 are SNEDDS of OFX with olive oil. OFXOAC1 to OFXOAC3 are SNEDDS of OFX with oleic acid oil. Table 1 details the composition of the SNEDDS, and Table 2 shows the optimized formulation of OFX-SNEDDS.

Table 1: Composition of SNEDDS.

Code	OFX (mg)	Oil (%)	Surfactants (%)	Co-surfactants (%)
OFXAO1	200	20	50	10
OFXAO2	200	30	40	10
OFXAO3	200	40	30	10
OFXPO1	200	20	50	10
OFXPO2	200	30	40	10

OFXPO3	200	40	30	10
OFXAR1	200	20	50	10
OFXAR2	200	30	40	10
OFXAR3	200	40	30	10
OFXOL1	200	20	50	10
OFXOL2	200	30	40	10
OFXOL3	200	40	30	10
OFXOAC1	200	20	50	10
OFXOAC2	200	30	40	10
OFXOAC3	200	40	30	10

Characterization of Ofx-Snedds

In-vitro dissolution studies

Following USP procedures, a dissolution test was conducted with 900 mL of water at $37 \pm 0.5^\circ\text{C}$, stirred at 50 rpm. Aliquots were carefully removed and replaced with fresh medium on a regular basis. The test used filters made of $0.45 \mu\text{m}$ PVDF paper, and ofloxacin concentration was measured using UV-spectrophotometry at 314.5 nm.

Microbial assay

Controlled organisms included bacterial isolates of *Bacillus cereus* and *Staphylococcus aureus*. A total of 28 grams of nutrient agar was prepared by dissolving it in 1000 milliliters of purified water. The agar was then sterilized in an autoclave at 121°C for 15 minutes (Pratiwi, 2021). Agar was poured into petri dishes and incubated at 37°C for 24 hours. The zone of inhibition was measured using the well-diffusion method, which involved placing equal concentrations of SNEDDS, OFXPO2 formulation, and the reference drug (Pratiwi, 2021).

Fourier Transform Infrared Spectroscopy (FT-IR)

Interactions between the API and excipients were analyzed using Fourier Transform Infrared Spectroscopy (FTIR). Both pure Ofloxacin and the optimized formulations were examined over the spectral range of 4000 to 500 cm^{-1} . The drug formulation with excipients showed no physicochemical interactions. Additionally, there were no significant differences in the wavelength (cm^{-1}) and functional groups (Asghar et al., 2022).

Droplet Size and Surface Charge

A five-milliliter volume of SNEDDS was carefully diluted with 1000 milliliters of water manually in a flask. The resulting emulsion was then analyzed for particle size distribution and zeta potential using laser diffraction with the Litesizer-500 Zetasizer. To measure the particle size, a sample was transferred into an Omega cuvette, and the data were recorded accordingly (Patel et al., 2011).

Data analysis

The release pattern of OFX was analyzed using one-way ANOVA, with a P-value under 0.05 regarded as statistically

significant.

RESULTS AND DISCUSSION

Construction of pseudo-ternary phase diagram

Surfactants, co-surfactants, and oils were used in varying proportions for phase studies. Tween 80 and PEG-400 were tested across multiple ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1) to modulate the HLB value and determine the self-nanoemulsifying region, resulting in a clear solution (Patel et al., 2011). Although co-surfactants offer benefits for nanoemulsions, excessive amounts can result in larger droplet sizes and a thicker interfacial film. The ideal surfactant to co-surfactant ratio was found to be 4:1 (Figure 2).

Solubility studies

The solubility of ofloxacin in various oils was determined by dissolving a considerable amount of the drug in each specific oil (13). The flask was then placed on a magnetic stirrer and kept stirred continuously for 24 hours at a consistent speed (13). After this period, the oils were collected and centrifuged at 6000 rpm for 10 minutes. The supernatant from each sample was subsequently extracted and diluted with methanol (25). Absorbance measurements were performed using a UV-spectrophotometer set at 314.5 nm, with methanol as the blank reference. The solubility of ofloxacin in oil was determined from the slope-intercept form of the calibration curve. The solubility in the tested oils is as follows: peppermint oil (81.98 mg/mL), almond oil (60.12 mg/mL), arachis oil (41.63 mg/mL), olive oil (41.48 mg/mL), and oleic acid (72.85 mg/mL). Peppermint oil exhibited the highest solubility at 81.98 mg/mL and was selected for further study (Lalwani et al., 2013; Senapati et al., 2016). We evaluated the solubility of various surfactants and co-surfactants, including Tween 20 at 35.48 mg/ml, Tween 80 at 183.37 mg/ml, Polyethylene glycol at 21.38 mg/ml, and Polyethylene glycol-400 at 183.33 mg/ml. Among these, Tween-80 and PEG 400 exhibited the highest solubility for ofloxacin (Lalwani et al., 2013; Namazi, 2025). Surfactants reduce the interfacial tension between the

two phases in an emulsion. The process was performed three times (figure 3).

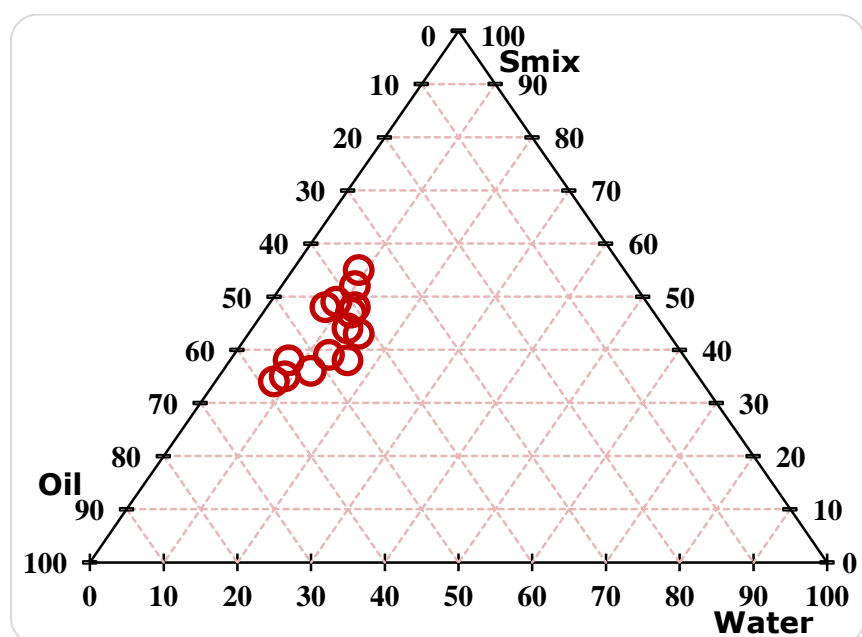


Figure 2: Pseudoternary phase diagram S_{mix} (4:1). (mean \pm SD, n=3).

Table 2: Composition of optimized SNEDDS formulation.

Ingredient	Nature	Qty
Ofloxacin	Active pharmaceutical ingredient	200mg
Peppermint oil	Oil	30%
Tween 80	Surfactant	40%
PEG-400	Co-surfactant	10%

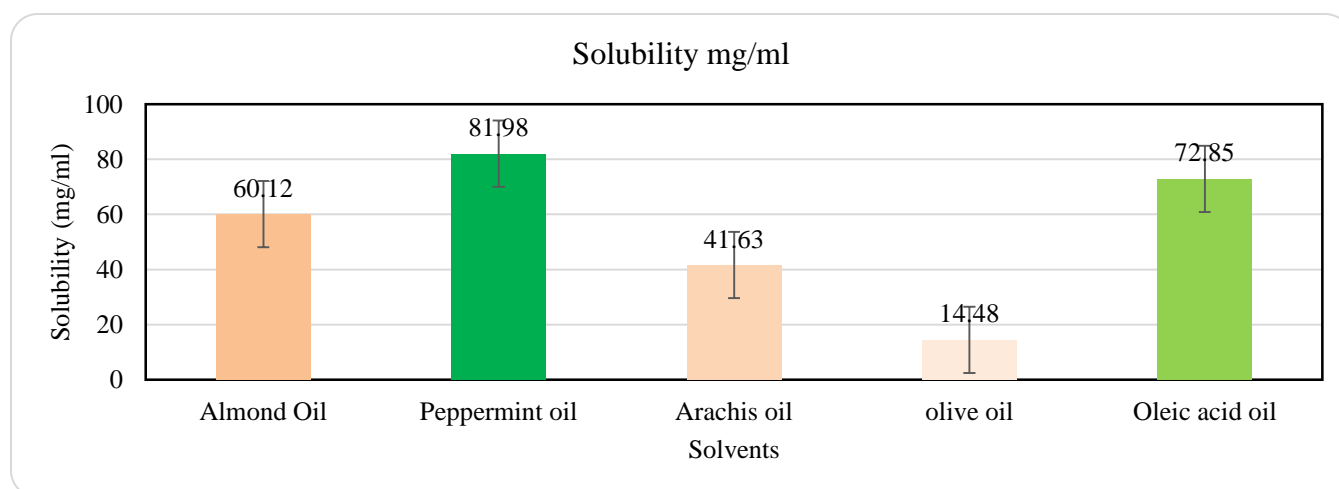


Figure 3: Solubility of Ofloxacin in various oils. (mean \pm SD, n=3).

Time of emulsification

Visual estimation is the primary method for assessing the ease of self-emulsification in SNEDDS. The extent of self-emulsification is primarily evaluated by measuring the rate of

emulsification, a critical indicator of emulsification efficiency. Specifically, when SNEDDS are introduced into an aqueous medium under gentle agitation, they should disperse completely and swiftly (Patel et al., 2011) (Table 3).

Table 3: Emulsification time, Zeta potential, PDI, Particle Size of SNEDDS formulations. (mean \pm SD, n=3).

Code	Particle Size (nm)	Polydispersity Index (PDI)	Zeta-potential (mV)	Time of emulsification (s)
OFXAO1	221.00 \pm 6.63	0.325 \pm 0.010	-9 \pm 0.27	108 \pm 3.24
OFXAO2	218.00 \pm 6.54	0.319 \pm 0.010	-11 \pm 0.33	102 \pm 3.06
OFXAO3	251.00 \pm 7.53	0.638 \pm 0.019	-7 \pm 0.21	97 \pm 2.91
OFXPO1	161.00 \pm 4.83	0.321 \pm 0.010	-15 \pm 0.45	82 \pm 2.46
OFXPO2	141.78 \pm 4.25	0.236 \pm 0.007	-17.9 \pm 0.54	73 \pm 2.19
OFXPO3	152.00 \pm 4.56	0.334 \pm 0.010	-16 \pm 0.48	84 \pm 2.52
OFXAR1	162.00 \pm 4.86	0.326 \pm 0.010	-10 \pm 0.30	99 \pm 2.97
OFXAR2	184.00 \pm 5.52	0.387 \pm 0.012	-16 \pm 0.48	102 \pm 3.06
OFXAR3	145.00 \pm 4.35	0.315 \pm 0.009	-12 \pm 0.36	104 \pm 3.12
OFXOL1	167.00 \pm 5.01	0.456 \pm 0.014	-13 \pm 0.39	106 \pm 3.18
OFXOL2	194.00 \pm 5.82	0.521 \pm 0.016	-11 \pm 0.33	120 \pm 3.60
OFXOL3	198.00 \pm 5.94	0.624 \pm 0.019	-10 \pm 0.30	124 \pm 3.72
OFXOAC1	201.00 \pm 6.03	0.625 \pm 0.019	-9 \pm 0.27	129 \pm 3.87
OFXOAC2	213.00 \pm 6.39	0.635 \pm 0.019	-9 \pm 0.27	128 \pm 3.84
OFXOAC3	270.00 \pm 8.10	0.725 \pm 0.022	-7 \pm 0.21	135 \pm 4.05

Dilution studies

In this study, distilled water was used as one of the dispersion media, and no significant difference was

observed. Nonionic surfactants for preparing nanoemulsions were diluted either in water, a phosphate buffer at pH 7.5, or at pH 1.2 (Patel et al., 2011) (Table 4).

Table 4: OFX-SNEDDS dilution studies. (mean \pm SD, n=3).

Code	Fraction	Buffer pH 1.2		Distilled water		Phosphate buffer pH 7.5	
		Immediately	After 24 hrs	Immediately	After 24 hrs	Immediately	After 24 hrs
OFXPO2	1:50	82	81	85	83	86	83
	1:100	88	86	90	91	91	89
	1:500	94	93	95	94	96	94

Release of OFX

The release of Ofloxacin from SNEDDS over two hours varied between 46% and 81%, as shown in figure 4. The OFX release was only 46% in the OFXAO1 formulation and reached up to 81% in the OFXPO2 formulation. The release rates for other formulations—OFXAR3, OFXPO3, OFXPO1, OFXAR1, OFXOL1, OFXAR2, OFXOL2, OFXOL3, OFXOAC1, OFXOAC2, OFXAO2, OFXAO1, and OFXAO3—were 77%, 75%, 73%, 64%, 63%, 60%, 58%, 56%, 54%, 53%, 51%, 49%, and 48%, respectively, over two hours. Formulations with medium levels of oils, surfactants, and co-surfactants showed superior OFX release compared to those with low or high PO concentrations (Villar et al., 2012). The R^2 values for zero-order release ranged from 0.561 to 0.901, indicating these followed first-order kinetics with R^2 between 0.990 and 0.999. The

Higuchi model's R^2 varied from 0.678 to 0.996. The Korsmeyer-Peppas model suggested non-Fickian diffusion when n was less than 0.45.

IR spectroscopy

Fourier transform infrared spectroscopy was performed to analyze the interaction between the drug and the polymer, focusing on the characteristic peaks of each component and their combinations. The stretching vibrations observed at specific peaks indicated the presence of chemical bonds and functional groups. The intensity of these peaks correlates with the relative abundance of the respective functional groups. Notably, Ofloxacin exhibited a peak at 1742 cm^{-1} , attributable to the stretching vibration of the carbonyl (C=O) functional group. Additionally, the presence of the carbon–nitrogen double bond (C=N) is indicated by a peak observed at 1615 cm^{-1} . Furthermore, the peak associated with the

carbon-sulphur bond (C-S) was recorded at 702 cm^{-1} (figures 5, 6).

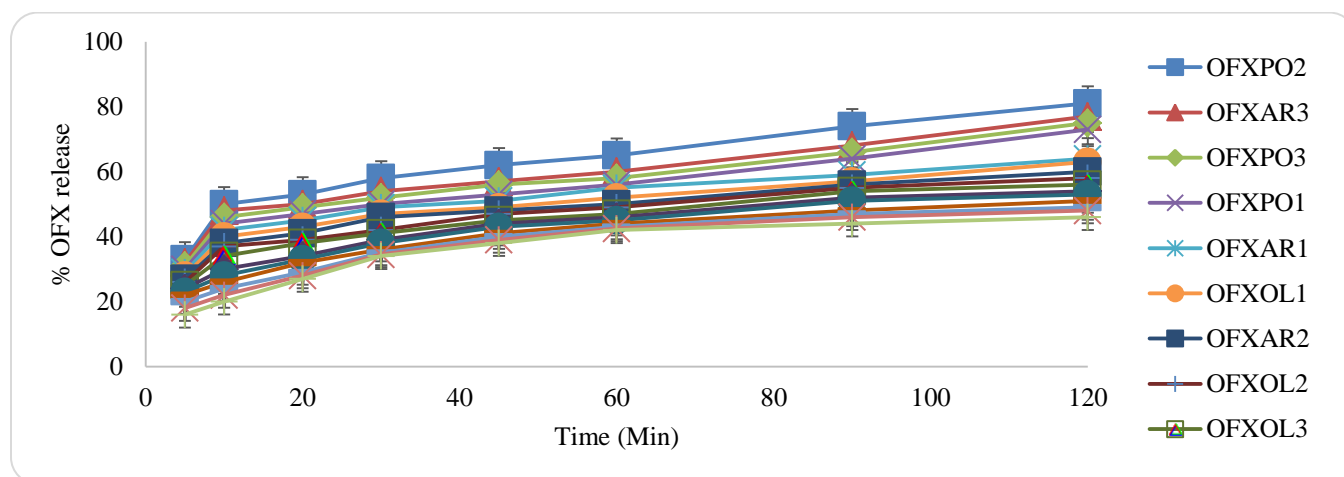


Figure 4: % OFX release from OFX-SNEDDS in 0.01 N HCl.

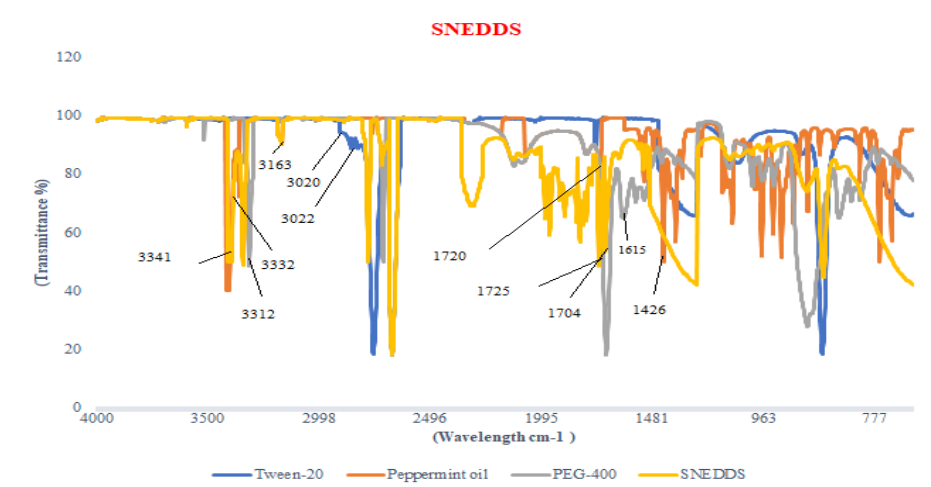


Figure 5: The spectra obtained from the Fourier Transform Infrared Spectroscopy (FT-IR) of SNEDDS demonstrate the components, including Tween 80, peppermint oil, PEG-400, and the SNEDDS formulation. (mean \pm SD, n=3).

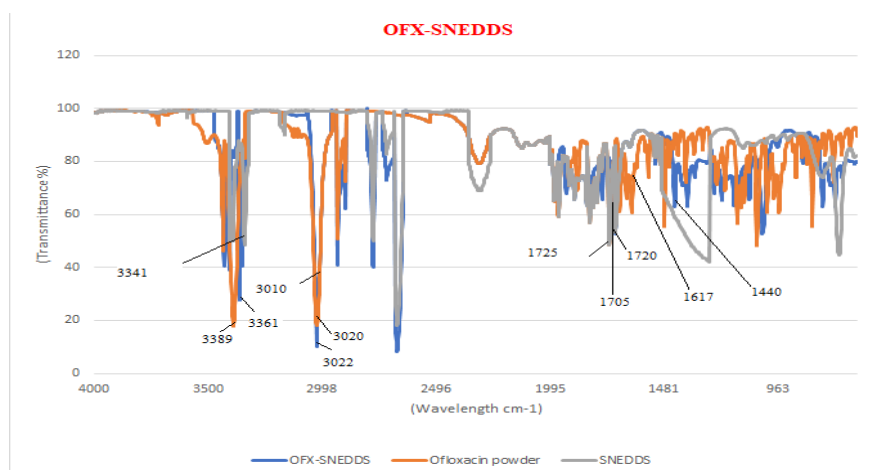


Figure 6: The FT-IR spectra of *Ofloxacin-SNEDDS* consist of both SNEDDS and the active pharmaceutical ingredient (API) of Ofloxacin. (mean \pm SD, n=3).

Determination of droplet size, zeta potential and PDI

The rate and amount of a drug released and absorbed depend on the size of the emulsion droplets, as this is a critical step in the self-emulsification process (Patel et al.,

2011). The particle size of the optimised formulation was determined to be 141.78 nm. SNEDDS having a polydispersity index of 0.186 and formulation OFXPO2 having 0.236. (Table 5), (Figures 7, 8, 9, 10).

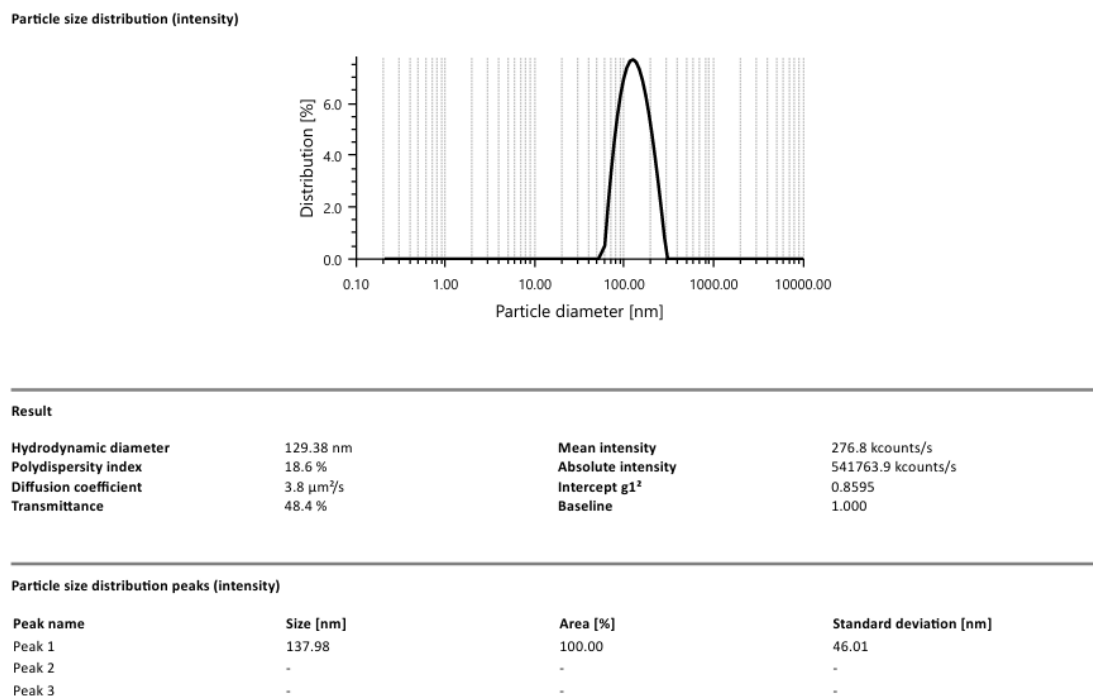


Figure 7: Particle Size of SNEDDS. The figure illustrates that the particle size of the SNEDDS formulation measures 137.98 nm before the drug is loaded. (mean \pm SD, n=3).

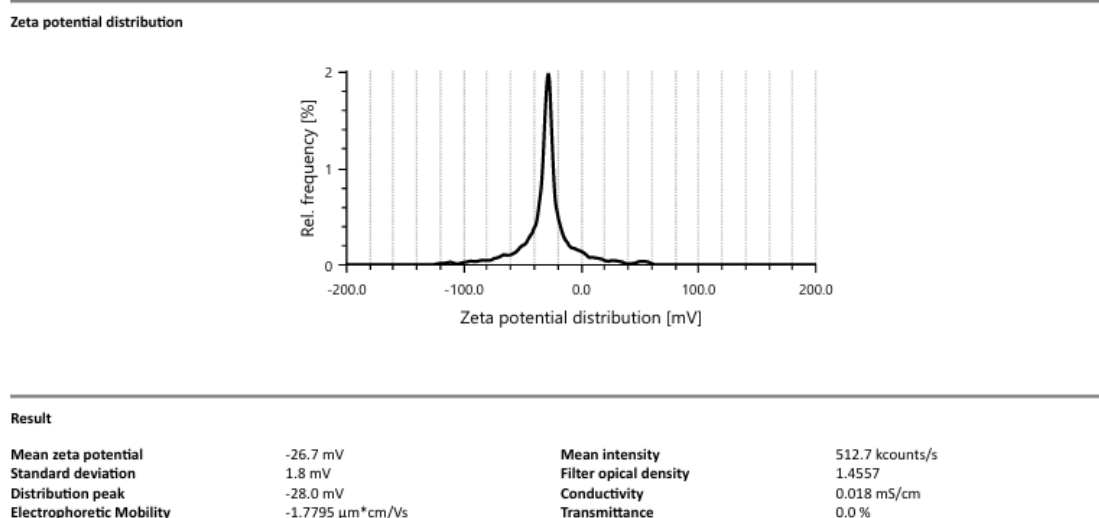
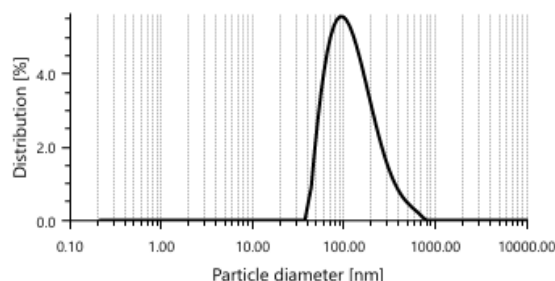


Figure 8: The zeta potential (mV) of SNEDDS is presented in the figure, which indicates that the zeta potential of SNEDDS is -26.7 mV. (mean \pm SD, n=3).

Particle size distribution (intensity)



Result

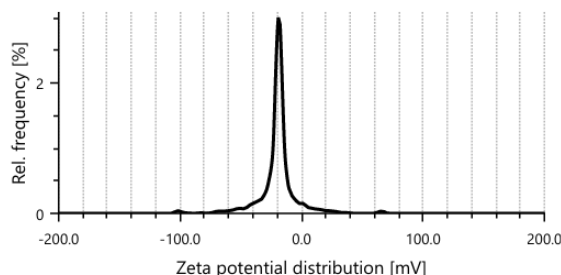
Hydrodynamic diameter	111.13 nm	Mean intensity	294.3 kcounts/s
Polydispersity index	23.6 %	Absolute intensity	291367.3 kcounts/s
Diffusion coefficient	4.4 $\mu\text{m}^2/\text{s}$	Intercept $g1^2$	0.8215
Transmittance	2.4 %	Baseline	1.000

Particle size distribution peaks (intensity)

Peak name	Size [nm]	Area [%]	Standard deviation [nm]
Peak 1	141.78	100.00	54.31
Peak 2	-	-	-
Peak 3	-	-	-

Figure 9: The figure illustrates that the particle size of OFX-SNEDDS measures 141.78 nanometers. (mean \pm SD, n=3).

Zeta potential distribution



Result

Mean zeta potential	-17.9 mV	Mean intensity	512.7 kcounts/s
Standard deviation	1.1 mV	Filter optical density	3.2071
Distribution peak	-18.7 mV	Conductivity	0.378 mS/cm
Electrophoretic Mobility	-1.1951 $\mu\text{m}^2/\text{cm/Vs}$	Transmittance	2.6 %

Figure 10: The zeta potential (mV) of OFX-SNEDDS is displayed in the figure, indicating that the zeta potential of OFX-SNEDDS is measured at -17.9 mV. (mean \pm SD, n=3).

Microbial assay

The antibacterial activity was evaluated using the agar well diffusion method. A bacterial suspension was added to sterile nutrient agar kept at 45°C, then allowed to solidify in a Petri dish. Each 90-mm Petri dish was poured with 20 mL of the medium on a level surface. After solidification, 4-mm-diameter wells were punched into the agar, with three wells evenly spaced from each other and the dish edge.

These wells contained 20 μL of SNEDDS, OFXPO2 formulation, and a reference drug. The dishes were incubated at 37°C for 24 hours in a controlled environment. After incubation, the zone of bacterial growth inhibition was measured with an accuracy of ± 0.1 mm. The average diameter of inhibition zones and the maximum variation were recorded. All tests were performed three times (Anwer et al., 2021). See figure 5.10 (a) and (b).

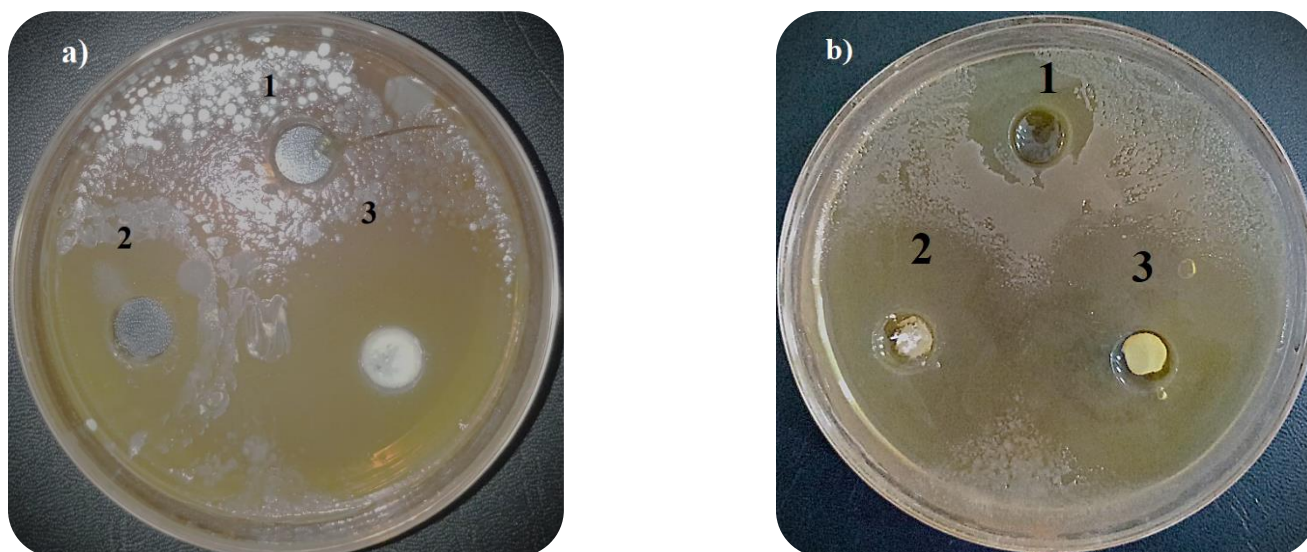


Figure 10 (a, b): a) Zone of inhibition of OFXPO2 formulation (3), SNEDDS before drug loading (1), Reference drug (2) respectively, b) Zone of inhibition of OFXPO1 formulation (3), SNEDDS before drug loading (1), Reference drug (2) respectively, (mean \pm SD, n=3).

CONCLUSION

In this study, SNEDDS of ofloxacin were successfully created and assessed for their in vitro performance. The nanoscale features of these formulations improve drug solubility and dissolution due to their large surface area. Their lipid-based composition aids in the delivery of drugs into the lymphatic system. The screening process for SNEDDS excipients, using the methodology employed, revealed differences in emulsification efficiency among various surfactants within the chosen oily phase. Incorporating SNEDDS with advancing nanotechnologies holds promise for enhancing drug delivery techniques and optimizing the overall therapeutic outcomes process. The optimized formulation needs further assessment in terms of toxicity and in- vivo pharmacokinetic profile.

FUNDING

This study did not receive any external funding.

CONFLICT OF INTEREST

The author states that there are no conflicts of interest.

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