



# Piroxicam Evaluation as a Drug Delivery System That Self-Emulsifies: Formulation and Characterization

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## Abstract

Piroxicam is an oxicam-class nonsteroidal anti-inflammatory medication used to treat gout, arthritis, and other inflammatory diseases (orally, topically). Because piroxicam is practically insoluble in water, the purpose of this research is to manufacture and test it as a liquid self-nano emulsifying system for delivering drugs in order to enhance its stability as well as dispersibility. For determining the optimum materials to dissolve piroxicam, dispersibility and stability study was undertaken in Oil, Surfactants, and Co-surfactants. Surfactants and co-surfactants ratios of (1:1, 2:1, 3:1, 4:1) were used to create pseudo ternary phase diagrams. There were additional four formulations made with different concentrations of Transcutol HP (diethylene glycol monomethyl ether), Cremophor EL (CrEL), and Triacetin oil. Dilution robustness, particle size distribution, drug content, dispersibility, and emulsification time are all factors to consider, and have all been examined in vitro. The self-nano emulsifying drug delivery system, according to the findings, is a practical technique to improve piroxicam dispersibility and stability.

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**Keywords:** Self-nano emulsifying; Surfactants; Transcutol HP; Triacetin; Drug delivery system.

## Introduction

About half of novel drug compounds have limited water solubility, and oral administration of these pharmaceuticals has revealed low bioavailability. Solid dispersions, cyclodextrin inclusion complex, micronization, lipids, surfactants, permeation enhancers, salt formulation, and nano-particles are only some of the formulation strategies now being used to overcome such issues [1-3]. The solubilization of the drug in colloidal dispersion will improve its availability and absorption. To encapsulate poorly soluble pharmaceuticals, physically stable formulations such as emulsion pre-concentrates, emulsions, and lipid solutions are extensively used [4].

Non-ionized dispersion or nanoemulsion pre-concentrates that are anhydrous, thermodynamically stable, and transparent or translucent are known as drug delivery systems that self-emulsify. When injected into aqueous phase under gentle agitation, anhydrous isotropic combinations of co-surfactant, surfactant, oil, and drug spontaneously form o/w nanoemulsions, usually with globule diameters smaller than 200nm, are regarded such systems [5-7].

The digestive motility of the gastrointestinal tract provides the agitation required to generate nanoemulsions in the body. SNEDDS aims to increase the oral-systemic absorption of drugs with low aqueous solubility by boosting colloidal dispersibility

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and retaining the drug dispersed in tiny oil globules throughout the gastrointestinal tract's transit [8,9].

Piroxicam is an oxycam-family a non-steroidal anti-inflammatory drug that is used in the treatment Gout and arthritis, in addition to some other inflammatory conditions (orally and topically). The bulk of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) work by stopping the production of prostaglandins [10,11]. It is substantially soluble in water and is also soluble in anhydrous ethanol and methylene chloride. According to Biopharmaceutical Classification System (BCS) parameters, piroxicam because it belongs to class II, meaning it has poor solubility and high permeability, the purpose of this research was to find out more about its formulate and evaluate piroxicam as a liquid (SNEDDS) to improve its stability, wettability, oil solubility, and colloidal dispersibility for the purpose of oral delivery.

## Materials and methods

### Materials

Hyperchem has delivered Piroxicam, Transcutol HP (diethylene glycol monomethyl ether), Cremophor EL (CrEL), and Triacetin oil. Sigma-Aldrich has provided the methanol. Avantor Performance Materials provided the Hydrochloric Acid (HCl).

### Tests on solubility

To find the optimal solvents for dissolving Piroxicam, a saturation solubility test was performed [12]. The solubility of Piroxicam has been tested in a variety of co-surfactants, oils, and surfactants. For each vial holding 2mL of the chosen vehicle, excessive amounts of Piroxicam powder were added. The mixture was sonicated for 3-5 minutes after which it was shaken for 48 hours at a temperature of 25°C in a water bath, according to the sealing process [13]. After that, they were centrifuged at 3000 RPM for 20 minutes, filtered through a Membrane Filter with a particle size of 0.45 µm, diluted with methanol as a solvent for dilution, and then spectrophotometrically analyzed for their drug contents at their respective Lambda max ( $\lambda$  max). The mean and Standard Deviation (SD) of the solubility results were determined.

### Pseudo-ternary phase diagram construction

Transcutol HP (diethylene glycol monomethyl ether), Cremophor EL (CrEL), and Triacetin oil were chosen as co-surfactant, surfactant, and oil phase, respectively, depending on the hydrophilic-lipophilic qualitatively and quantitatively and solubility research findings. The Pseudo-Ternary Phase Diagram was created using a water titration technique to determine the ratios of Drug Delivery System with Self-Nano Emulsification (SNEDDS) components [14,15]. Surfactants and their co-surfactants mixtures (Smix) have been mixed in various proportions (1:1, 2:1, 3:1, 4:1). The surfactant combination under mild magnetic agitation, the oil mixture was gradually determined by titration with distilled water till a stable, transparent system was produced, and the transition from transparent to turbidity point was noted down. The information gathered was used to create a ternary plot using CHEMIX School Software.

### Piroxicam liquid preparation as a drug delivery system that self-nano emulsified

In a series of liquid formulations of Self-Nano Emulsifying Drug Delivery Systems (SNEDDS) (1:1, 2:1, 3:1, 4:1), Triacetin was utilised as an oil, Cremophor EL (CrEL) like an surfactant, in addition to Transcutol HP (diethylene glycol monomethyl ether)

like an co-surfactant: Smix ratio. As seen in Table 1, the Smix ratio of 2:8 remains constant.

**Table 1:** SNEDDS of piroxicam liquid composition (weight per weight percent).

Code – formula	Smix ratio	Oil: Smix ratio	Triacetin oil%	CrEL%	Transcutol HP%
SNEDDS -1	01:01	2:08	20	40	40
SNEDDS -2	02:01			53.33	26.66
SNEDDS -3	03:01			60	20
SNEDDS -4	04:01			64	16

Piroxicam was dissolved in oil into a glass screw cap, then mixed with other components at a concentration of 10 mg/0.4 mL, and heated in a water bath to homogenize the mixture. The components were mixed for 5 minutes in a vortex mixer to achieve a homogenous and clear mixture, which was then allowed to cool at room temperature before being sonicated for 10 minutes at room temperature. Before the droplet size distribution study, the formulations were held under visual inspection for a minimum of 48 hours and evaluated for turbidity or phase separation [16-18].

### Evaluations of piroxicam liquid that has been prepared (SNEDDS)

#### Examinations of thermodynamic stability

The liquids that have been prepared in the formulations of SNEDDS have been put through a series of thermodynamic stability evaluations (centrifugation, cooling-heating cycles, in addition to freeze-thaw cycles). The formulations that are stable have been chosen for the heating-cooling cycle after centrifugation at 3500 RPM for 30 minutes and inspection for cracking, creaming, phase separation, and precipitation [19,20]. Formulations that seem to be stable at these temperatures have been subjected to a freeze-thaw cycles between 4°C - 45°C into the refrigerator, with at least 48 hours of storage at each temperature. There are 3 freeze-thaw cycles, each lasting at least 48 hours, between (-21°C - 25°C) at each one of temperature storage. The generated formulations have been offered for further research after passing thermodynamic stress testing.

#### Polydispersity index (PDI) and droplet size measurements

By dissolving 0.5 mL of the liquid formula in 250 mL distilled water and gently mixing by a magnetic stirrer at 25°C, all the stable formulations were submitted to a mean droplet size and Polydispersity Index (PDI) test. A particle size analyzer device was used to assess droplet size and PDI, and light scattering was recorded at a temperature of 25°C at a 90° angle [21,22].

#### Dilution robustness

In two separate glass vials, the prepared SNEDDS with distilled water, the compositions were diluted 50, 100, 1000, then 3000 fold and 0.1N HCl. The resulting diluted nanoemulsion formulations were shaken and then visually examined after 24 hours for any indications of drug precipitation or phase separation droplet coalescence [23,24].

#### Self-emulsifying time and dispersibility tests

The efficiency of USP Dissolution Apparatus 2 [25,26] in terms of dispersibility and self-nano emulsification time has been assessed. Each of the SNEDDS formulations was introduced in an

amount of roughly 0.5 mL to 500 mL of distilled water held at 37°C 0.5°C with gentle agitation at 50 RPM. As shown in Table 2, in vitro efficiency, was visually seen when generating a transparent homogeneous system and determining time in minutes to achieve complete nano-emulsification using a grading system.

**Table 2:** The SNEDDS in vitro performance grading system (Dispersibility and self-Nano emulsification time).

Grade	The time it takes to make a nano-emulsion	Appearance
A	Forming quickly (within one minute)	Have a blue or transparent appearance
B	Swiftly forming (within one minute)	Emulsion with a less clear bluish-white appearance
C	Within 2 minutes, it was formed	Fine milky emulsion
D	Slow emulsification (longer than two min.)	Emulsion with a dull, greyish white look and a somewhat oily appearance
E	Slowly emulsify (more than two minutes)	With large oil globules on the surface, this emulsion has poor or minimal emulsification

### Determination of drug content

Each SNEDDS formulation's drug concentration was determined using spectrophotometric estimation within UV [27], and 0.4 milliliters (equivalent to 10-milligram Piroxicam) from each created formulation was diluted to 100 milliliters with methanol and properly mixed. The predicted Lambda max ( $\lambda$  max) was used to evaluate the resulting solutions [28].

### In-vitro analysis of dissolution

The *in vitro* drug release of pure Piroxicam powder and produced SNEDDS formulations was evaluated using the USP Dissolution Apparatus 2, with adjusted dissolution settings (paddle at 50 RPM, 900 mL 0.1 N HCl) and the dialysis bag technique Da Cutoff for Molecular Weight (MWCO/12000 Da) [25,29]. The SNEDDS formulations were rinsed with deionized water to remove preservatives and then steeped overnight in a dissolving media of 0.1 N HCl to achieve equilibration [30]. A dialysis bag was filled with a liquid SNEDDS formula containing one dose of Piroxicam, and 5 milliliters of the dissolving medium were withdrawn every 10 minutes for 60 minutes (10, 20, 30, 40, 50 and 60) and replaced with new media 0.1 N HCl in each withdrawal. The amount of dissolved medication was determined using a UV-Spectrophotometer method at its Lambda max (max) value [31].

### Formulation of the best piroxicam liquid self-nanoemulsion

The optimal Piroxicam liquid SNEDDS formula was chosen based on the assessment tests (droplet size, PDI, in vitro dissolving testing, and drug content).

### Infrared spectroscopy using the fourier transform (ftir)

The KBr Disc technique was used to record the infrared spectra of Piroxicam and a specified liquid SSNEDDS formula. Its primary purpose is to determine component compatibility and the presence of interactions [32,33]. The powder sample was combined with KBr and finely ground before being compressed onto a KBr disc. All KBr discs were scanned in the 400  $\text{cm}^{-1}$ -4000  $\text{cm}^{-1}$  wavenumber range.

### Field emission scanning electron microscopy (fe-sem)

The morphology was examined using FE-SEM. of the selected liquid SNEDDS formula. FE-SEM was used to examine a tiny amount of the nanoemulsion sample [34]. The samples were inspected at various magnifications, with data collection of the images into personal computers taking place in real-time.

### Statistical analysis

The One-way laboratory analysis of variance was used to

analyse the experimental statistics at the level of ( $P < 0.05$ ) as well as expressed as the standard deviation of three duplicate samples to see if the changes in the applied components were  $P < 0.05$  is statistically considerable, while  $P > 0.05$  is non-considerable.

## Results & discussions

### Saturation solubility

Piroxicam has been tested for solubility in a variety of co-surfactants, surfactants, and oils, including those mentioned in Table 3 where Piroxicam dissolves readily in Triacetin oil. The greatest solubility of Piroxicam was observed with the surfactant Cremophor EL (CrEL) and co-surfactant Transcutol HP, as shown in Table 4.

**Table 3:** Values of piroxicam saturation solubility in various oil types.

Oil type	Solubility value (mg/mL) Mean $\pm$ SD*	Oil type	Solubility value (mg/mL) Mean $\pm$ SD*
Coconut	8.32 $\pm$ 0.066	Triacetin	48.10 $\pm$ 0.057
Sunflower	2.35 $\pm$ 0.11	Corn	2.38 $\pm$ 0.14
Peppermint	4.60 $\pm$ 0.047	Paraffin	0.41 $\pm$ 0.067
Castor	0.79 $\pm$ 0.089	Linseed	1.15 $\pm$ 0.035
Oleic acid	11.86 $\pm$ 0.093	Avocado	1.21 $\pm$ 0.027
Olive	2.06 $\pm$ 0.032	Almond	0.69 $\pm$ 0.041
Sesame	2.33 $\pm$ 0.079	Jajoba	0.64 $\pm$ 0.023
Cinnamon	8.64 $\pm$ 0.051	Aniseed	2.07 $\pm$ 0.072

\*SD: Standard Deviation from the Mean; n=3

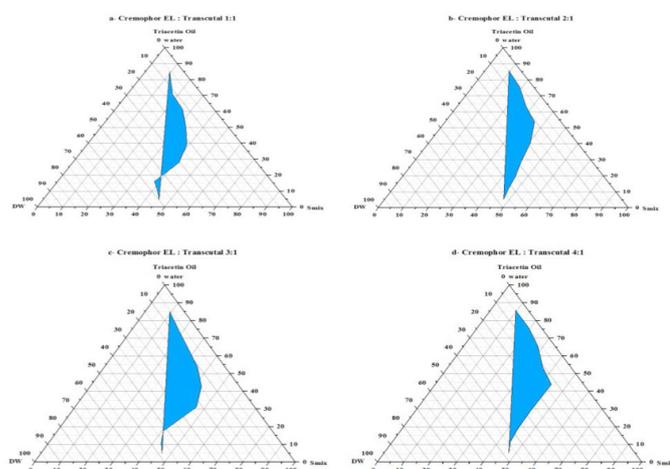
**Table 4:** Piroxicam saturation solubility in surfactant and co-surfactant types.

Surfactant Type	Solubility Value (mg/mL) Mean $\pm$ SD*	Co-Surfactant Type	Solubility value (mg/mL) Mean $\pm$ SD *
Span 20	2.018 $\pm$ 0.019	Transcutol HP	30.9 $\pm$ 0.062
Span 80	1.88 $\pm$ 0.089	PEG 200	4.63 $\pm$ 0.048
Tween 20	1.28 $\pm$ 0.13	PEG 400	10.59 $\pm$ 0.12
Tween 40	0.91 $\pm$ 0.086	PEG 600	2.54 $\pm$ 0.023
Tween 60	8.61 $\pm$ 0.11	Ethylene glycol	0.61 $\pm$ 0.038
Tween 80	6.17 $\pm$ 0.093		
CrEL	33.7 $\pm$ 0.054		

\*SD: Standard Deviation from the Mean; n=3

### Pseudo-ternary phase diagram

For identifying self-emulsifying regions and SNEDDS formulations, diagram of a pseudo-ternary phase have been produced. Diagram of a pseudo-ternary phase plot for various Smix ratios (Cremophor EL (CrEL): Transcutol HP 1:1, 2:1, 3:1, and 4:1. Figure 1 depicted a pseudo-ternary phase diagram; the shaded region shows the area of nanoemulsions, whereas the unshaded area represents the area of the emulsion. The plot with a bigger shaded region suggests that the created nanoemulsions have ideal nano-emulsifying activity and good interaction between the Smix, oil, and aqueous phase [35]. Even after infinite water titration or dilution, the oil: Smix 1:9 and 2:8 ratios remained as nanoemulsions. This is possible because CrEL with Transcutol HP mixture is hardly localized on the surface in terms of nano-emulsion droplets, lowering interfacial free energy and providing a mechanical barrier to coalescence, causing automatic dispersion. The presence of excellent nano-emulsifying activity of formed nanoemulsions is shown by the ratio of CrEL rise, which demonstrated the best nano-emulsification properties [36-38].



**Figure 1:** For various Smix ratios, the diagram plots the pseudo ternary phase (CrEL: Transcutol HP 1:1, 2:1, 3:1, 4:1).

### Piroxicam liquid (SNEDDS)

Visual inspection of all liquid Piroxicam (SNEDD) formulae revealed yellow and transparent mixes. There is no dispersed phase or drug precipitation in this method.

### Thermodynamic stability

At the end of each cycle, there were no evidence of drug precipitation or processing conditions, hence all of the Piroxicam (SNEDDS) formulations were approved the thermodynamic stability examinations. This showed that formulations can withstand storage in harsh environments.

### Droplet size and PDI measurements

Table 5 displays the droplets as well as PDI values. The size of the droplet nanoemulsions is an important issue during self-emulsification since its affects the amount as well as drug speed of release in addition to drug absorption [39]. Size of a droplet related to prepared SNEDDS formulations was (29.6 nm-112.7 nm), with a PDI of around 0.3, compared to (SNEDDS-1) of 0.551. A PDI of less than 0.3 indicates the best consistency in droplet size dispersion after dilution with water [40,41].

**Table 5:** Drug delivery size of the droplet, Polydispersity Index measurements.

Code – formula	Size of Droplet, nm	Poly dispersity Index
SNEDD-1	112.7	0.551
SNEDD-2	29.6	0.312
SNEDD-3	66.7	0.379
SNEDD-4	41.1	0.262

### Dilution robustness

All of the Piroxicam (SNEDDS) formulations passed the test, with no phase separation visible. Capacity of SNEDDS formulation to maintain aqueous dilution has been exceptional. It was attributed to the capacity of excipients to generate stable nanoemulsions with small droplet sizes, as well as their high solubilizing properties. This suggests that such formulations were stable at infinite water dilution and had great dilution robustness [16,42].

### Self-emulsifying time and dispersibility tests

The difference in self-emulsification timings of various formulas in bulk liquid SNEDDS was extremely small, and because observation times were fast (in seconds), it was impossible to discriminate between the produced formulas [43,44].

### The presence of drugs

All generated Piroxicam (SNEDDS) was greater than 96 percent, with no significant differences between formulations ( $p > 0.05$ ), which met USP standards and fell within an acceptable range (90 percent - 110 percent) [45,46], as shown in Table 6.

**Table 6:** Piroxicam liquid self-nanoemulsion drug content percent.

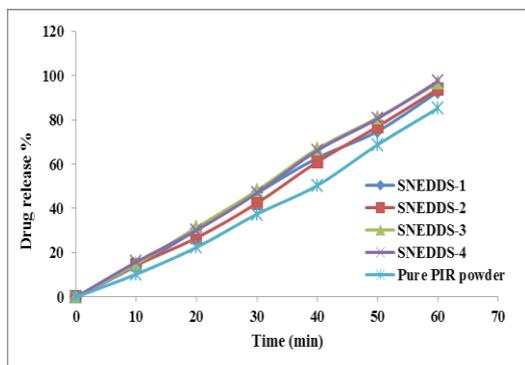
Code – Formula	Drug Content % Mean $\pm$ SD*
SNEDDS-1	99.61 $\pm$ 0.078
SNEDDS-2	96.82 $\pm$ 0.14
SNEDDS-3	97.50 $\pm$ 0.084
SNEDDS-4	98.24 $\pm$ 0.061

\*SD: Standard Deviation from the Mean; n=3

### In-vitro analysis of dissolution

According to Figure 2, the produced Piroxicam (SNEDDS) formulations released more than 92 percent of the drug after 60 minutes, whereas SNEDDS-4 released 97 percent. Because the drug is dissolved, the faster release is due to small particle size and high surfactant combination concentrations, which may simply emulsify oil for finer globules.

Pure Piroxicam has a slower release profile than prepared Piroxicam (SNEDDS) formulae, reaching 85 percent after 60 minutes without the use of a dialysis membrane. The extent and rate release profiles of all the created SNEDDS formulations are not statistically significant ( $P > 0.05$ ) yet they are significantly different from the extent and rate release profile of ordinary Piroxicam powder ( $P < 0.05$ ). Finally, the SNEDDS preparations result in the spontaneous formation of nanoemulsions of tiny droplet sizes, allowing for considerably quicker release of the drug into the aqueous solution than pure drug powder.



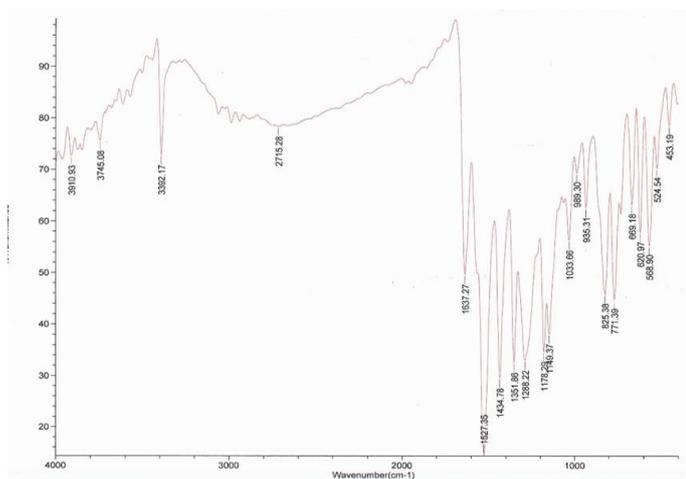
**Figure 2:** Piroxicam (SNEDDS) and Pure Piroxicam dissolution profiles.

**Optimum piroxicam liquid self-nanoemulsion**

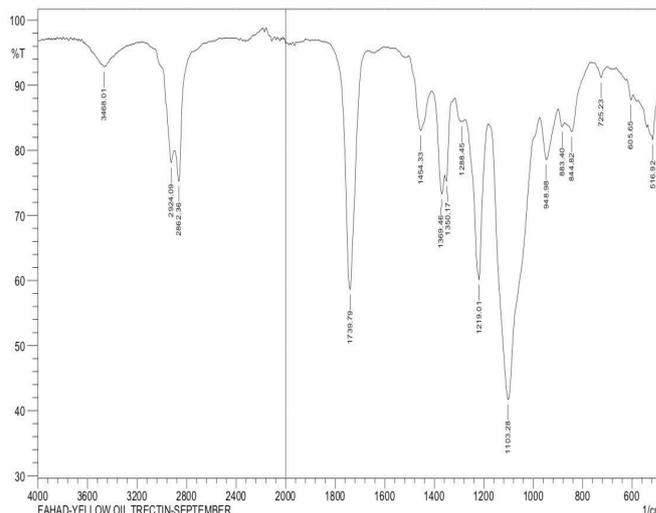
Because SNEDDS-4 had a larger drug content, higher *in vitro* release. It was picked as the best Piroxicam liquid self-nanoemulsion because of its smaller droplet size and lower PDI value.

**Fourier transforms (FTIR)**

Figures 3 and 4 show the FTIR spectra of Piroxicam and the selected formula SNEDDS-4, respectively. The secondary amine N-H stretching peak was found at  $3392.17\text{cm}^{-1}$  in FTIR spectrum of Piroxicam [47,48]. Piroxicam has two interconvertible crystalline forms, the needle, and cubic forms, according to reports. The stretching of amide carbonyl groups in the needle and cubic forms of piroxicam is assigned to the IR absorption peaks at  $1634\text{cm}^{-1}$  and  $1629\text{cm}^{-1}$ , respectively. For both crystalline forms of piroxicam, the peak at  $1527.35\text{cm}^{-1}$  is due to the stretching of the second amide band. The peak at  $1637.27\text{cm}^{-1}$  in the IR spectrum of Piroxicam was discovered in this investigation, indicating that the needle form of piroxicam was employed [49-51]. The piroxicam spectra also exhibited other characteristic peaks like, Aromatic C-C Stretches at  $1434.78\text{cm}^{-1}$ , C-N stretching at  $1351.86\text{cm}^{-1}$ , C-O stretching at  $1288.22\text{cm}^{-1}$ , S(=O)<sub>2</sub> stretching at  $1149.37\text{cm}^{-1}$ , -SO<sub>2</sub>-N stretching at  $1033.66\text{cm}^{-1}$ , C-H Bending at  $825.38\text{cm}^{-1}$ , ortho-Disubstituted Phenyl at  $771.39\text{cm}^{-1}$  and C-S stretching at  $669.18\text{cm}^{-1}$ , which indicate the purity of the drug [52,53]. According to the FTIR data, there were no differences in the peaks of the piroxicam spectrum compared to the spectra of the specified formula SNEDDS-4, indicating that there were no chemical interactions between the piroxicam and the excipients used in the formulation.



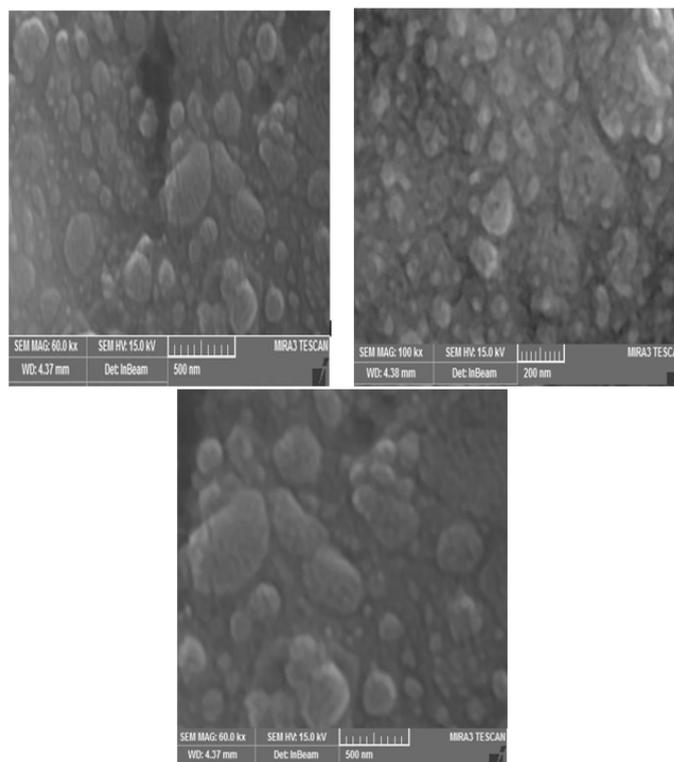
**Figure 3:** Piroxicam’s FTIR spectrum.



**Figure 4:** FTIR spectra of a particular Piroxicam formulation (SNEDDS-4).

**FE-SEM**

Under the FE-SEM, the liquid SNEDDS-4 was observed, and the results are depicted in Figure 5. The obtained result indicated that the droplet was about spherical in shape.



**Figure 5:** FE-SEM images of SNEDDS-4.

**Conclusions**

According to the findings of this study, Piroxicam (SNEDDS), which was made from Triacetin oil, Cremophor EL (CrEL), in addition to Transcutol HP, has made available an important dosage form for oral water-insoluble drugs, as well as a significant strategy for improving stability, wettability, solubility, and dissolving rate. *In vitro* performance of Piroxicam (SNEDDS) has been successfully developed and analyzed. Because of the enormous area of the surface available for drug absorption as well as release, the nanosize of such formulations improves drug solubility.

## Declarations

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**Conflict of interest:** The authors declare that they do not seek monetary benefits or individual associations that may have come into play in order to influence the performance described in this article.

**Disclosure statements:** The authors declare that they have no financial or personal interests that could appear to have influenced the work described in this paper.

**Author's contributions:** Dr.Zahra Al-Timimi: Conceptual model, Methods, Original Draft Writing, Writing Review and also Editing, Investigation. Dr. Zeina J Tammemi: Validation, Data collection, critical examination, tools, project administration.

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**Availability of data and materials:** The data that support the findings of this study are available on request from the corresponding author.

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