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Nanoemulsifying Drug Delivery System to Improve the Bioavailability of Piroxicam

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Abstract

Objective: The aim of this study is to develop and characterize self-nanoemulsifying drug delivery system (SNEDDS) of piroxicam in liquid and solid forms to improve its dissolution, absorption and therapeutic efficacy.

Materials and methods: The generation of liquid SNEDDS (L-SNEDDS) was composed of soybean or coconut oil/Tween 80/Transcutol HP (12/80/8%w/w) and it was selected as the optimized formulation based on the solubility study and pseudo-ternary phase diagram. Optimized L-SNEDDS and liquid supersaturatable (L-sSNEDDS) preparations were then adsorbed onto adsorbents and formulated as directly compressed tablets.

Results and discussion: The improved drug dissolution rate in the solid supersaturatable preparation (S-sSNEDDS) may be due to the formation of a nanoemulsion and the presence of drug in an amorphous state with hydrogen bond interaction between the drug and SNEDDS components. In vivo pharmacokinetic studies on eight healthy human volunteers showed a significant improvement in the oral bioavailability of piroxicam from S-sSNEDDS (F12) compared with both the pure drug (PP) and its commercial product (Feldene®) (CD). The relative bioavailability of S-sSNEDDS (F12) relative to PP or CD was about 151.01% and 98.96%, respectively.

Conclusion: The obtained results ratify that S-sSNEDDS is a promising drug delivery system to enhance the oral bioavailability of piroxicam.

Keywords:
Oral, piroxicam, self-nanoemulsifying system, particle size, surfactants.
Introduction

Piroxicam is a member of the oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of musculoskeletal, joint and other inflammatory disorders. It is proposed as a class II drug with low solubility (Pka 6.3) and high permeability according to the Biopharmaceutic Drug Classification System (BCS) (1). It binds strongly to plasma protein (>99%) rendering a prolonged therapeutic action. However, it reaches a maximum concentration within three to five hours after oral administration which delays its onset of analgesic and anti-inflammatory effect (2). Whereas, the majority of pain treatment therapies require a rapid onset of action to achieve an acute analgesic effect.

Several techniques were carried out on piroxicam to improve its dissolution, bioavailability and decrease its side effects such as gastric irritation. These techniques include; microemulsion (3), solid lipid microparticles (4), solid dispersion (5,6), nanostructured lipid carrier (7), cogrinding (8), self-emulsifying pellets (9) and lipid formulations (10).

Self-nanoemulsifying drug delivery system (SNEDDS) is the advanced technology of lipid based drug delivery system due to its ability to improve the oral bioavailability of lipophilic drug (11,12). It is a translucent, anhydrous isotropic mixture of oil, surfactant and co-surfactant that is readily dispersed in the aqueous environment of the GIT to produce fine oil in water nanoemulsions. When compared with conventional metastable emulsions, SNEDDS is a thermodynamically stable formulation with high solubilization capacity for lipophilic drugs (13,14). There are several mechanisms of SNEDDS for enhancing drug absorption and its bioavailability such as circumventing the hepatic portal route, facilitating lymphatic transport of drugs, protection from drug degradation in the GI, reducing cytochrome P450-induced metabolism in the liver and inhibiting the P-glycoprotein mediated efflux (15-17). On the other hand, its limited stability and risk of drug precipitation following dilution often hinders its pharmaceutical application. In order to inhibit drug precipitation after the
dispersion of SNEDDS in the GIT, the supersaturatable SNEDDS (sSNEDDS) was used that contains a water-soluble polymeric precipitation inhibitor (PPI) in addition to the typical composition of SNEDDS. The PPI retards excessive drug precipitation following dilution and maintains a temporary supersaturated state (18,19). Furthermore, it is important to convert these liquid supersaturatable preparations into solid forms with higher stability, better transportability, and better patient compliance as well as for simplicity and cost effectiveness in their manufacturing (20).

The main objectives of the current study are to develop and optimize piroxicam-SNEDDS formulations in liquid and solid dosage forms. They were evaluated for both in vitro drug release characteristics and in vivo study.

Materials and methods

Materials

Piroxicam was supplied by Medical Union Pharmaceuticals (MUP) Co., Egypt. Corn oil, liquid paraffin, soybean oil, ethyl oleate, olive oil, coconut oil, polyethylene glycol 400 (PEG 400), colloidal silica (Aerosil 200), microcrystalline cellulose (Avicel PH 101) and hydroxypropyl methylcellulose-E15 (HPMC-E15) were purchased from Sigma-Aldrich Co., Ltd., Germany. Transcutol HP and labrasol were obtained as gift samples from Gattefosse Co., Saint-Priest Cedex, France. Tween 20, Tween 60, Tween 80, propylene glycol, absolute ethyl alcohol, sodium phosphate dibasic and potassium di-hydrogen phosphate were obtained from El-Nasr Pharmaceuticals and Chemicals Co., Egypt. Cremophor® EL and cremophor® RH 40 were procured as generous gift samples from BASF Corp. (Ludwigshafen, Germany). Acetonitrile and methanol (HPLC grade) were purchased from Fisher Scientific, UK. All other chemicals and solvents were of analytical grade.
Methods

Solubility study of piroxicam using oils and surfactants

Solubility of piroxicam was determined in different excipients viz. oils (Corn oil, Liquid paraffin, Soybean oil, Ethyl oleate, Olive oil and Coconut oil), surfactants and co-surfactants (Tween 20, Tween 60, Tween 80, Labrasol, Cremophor® EL, Cremophor® RH40, Transcutol HP, Propylene glycol and PEG400). Excess amount of piroxicam powder (about 0.5 g) was added to each vial containing 2 ml of the selected vehicle. After sealing, the mixtures were vortexed for 10 min and then shaken for 3 days in a water bath shaker (Grant instrument Cambridge Ltd., Barrington Cambridge, England) at 37 ± 0.5°C at 50 rpm. They were then centrifuged at 5000 rpm for 5 min, followed by filtration through 0.45 µm membrane filter, diluted with methylene chloride and assayed spectrophotometrically at 333 nm for their drug contents using a blank of drug-free excipients treated in the same manner (21). Solubility experiment was triplicated and the results were calculated as mean ± SD.

Construction of pseudo-ternary phase diagrams

Regarding the results of solubility studies, soybean oil or coconut oil, Tween 80 and Transcutol HP were selected as oil phase, surfactant and co-surfactant, respectively. Pseudo-ternary phase diagram was constructed to determine the ratios of SNEDDS components at ambient temperature (25°C) using water titration method (22). Surfactant and co-surfactant (S/CoS) were mixed in different weight ratios (1:1, 1:2, 2:1, 3:1, 4:1, 5:1 and 10:1). For construction of each phase diagram, oil and S/CoS were mixed thoroughly in different weight ratios starting from 1:9 to 9:1 in different glass vials which is then titrated by water in order to precisely delineate the boundaries of phase diagrams (23). The experiment was triplicated (mean ± SD).
Preparation of self-emulsifying formulations

Preparation of liquid SNEDDS

Regarding pseudo-ternary phase diagram, series of SNEDDS were prepared using either soybean or coconut as the oil phase, Tween 80 as a single surfactant or in combination with 5% PEG 400 as mixed surfactants and Transcutol HP as a co-surfactant (20). Accurately weighed quantities of oil, surfactant and co-surfactant were vortexed in a glass vial for 30 sec to get a clear homogenous mixture then, 4% w/w piroxicam was added and dissolved using a magnetic stirrer and heating at 40°C. The obtained L-SNEDDS (equivalent to 10 mg drug) were packed into a size 0 hard gelatin capsules which were then sealed and stored in glass bottles at 25°C until used for further studies.

For preparing L-sSNEDDS, 5% w/w HPMC-E15 was added to a series of L-SNEDDS in glass vials. The mixtures were mixed for 5 min using a cyclo-mixer (CM101, Remi, Mumbai, India) to get uniform suspensions.

Preparation of SNEDDS-loaded tablets

Ten grams of each L-SNEDDS or L-sSNEDDS were homogenously blended with a mixture of Aerosil 200: Avicel PH 101 (ratio 1:1) and superdisintegrant (Ac-Di-Sol) (Table 1) to form solid SNEDDS (S-SNEDD) and S-sSNEDDS, respectively. The resultant powder mixture was stirred until a freely flow, non-sticky solid powder was formed. The resultant powder was sieved through sieve No.60 (pore size 250 µm) to break down any lumps or agglomerates. The average weight of the tablets was about 625-715 mg (equivalent to 10 mg drug) for S-SNEDDS and S-sSNEDDS, respectively. They were prepared by direct compression method using a single punch tablet machine (Erweka-Apparate, G.M.B.H., E.K.O., Germany).
Table 1 showed the composition of piroxicam loaded self-nanoemulsifying formulations where F2-F3, F5-F6, F8-F9 and F11-12 are S-SNEDDS and S-s SNEDDS for F1, F4, F7 and F10 L-SNEDDS, respectively.

_Evaluation of L-SNEDDS_

_Stability study_

_Robustness to dilution._ Robustness is the stability of SNEDDS upon high dilution with water. The study was performed by diluting the drug-loaded SNEDDS with distilled water in a ratio 1:100 and storing for 12 hr then the system was observed for phase clarity, drug precipitation and self-emulsification time. Three runs were carried out for each preparation (24).

_Thermodynamic stability._ Self-nanoemulsifying systems were subjected to different stress conditions including; heating/cooling, freeze/thaw and centrifugation stresses (25). During this study, drug-loaded SNEDDS were subjected to heating and cooling cycles by heating to 45°C followed by cooling to 4°C. Preparations were maintained at each temperature for 45 hr and this cycle was repeated three times. The freeze/thaw stress study was performed by subjecting them to freezing at -4°C for 12 hr followed by storing at 4°C for a further 12 hr. Moreover, centrifugation stress study was conducted by subjecting the preparations to centrifugation at 3000 rpm for 30 min. After each stress study the preparation was examined for phase separation and drug precipitation.

_Droplet size, zeta potential and pH measurements_

Droplet size and polydispersity index (PDI) of the nanoemulsions produced from aqueous dilution of L-SNEDDS and L-sSNEDDS were determined by photon correlation spectroscopy (Zetasizer, Nano-ZS 90, Malvern, UK) using dynamic light scattering technique. One milliliter of drug-loaded SNEDDS was diluted to 25 ml with distilled water and shaken gently to form a nanoemulsion then subjected to particle size measurement using zetasizer.
The zeta potential of the nanoparticles was measured using the laser doppler velocimetry technique of the zetasizer by placing the diluted sample in an electrophoretic cell until a potential of 150 mV was established (26). Three replicates were carried out for each preparation and the data was calculated as mean ± SD. The pH values of piroxicam L-SNEDDS and L-sSNEDDS preparations were determined at 25°C using digital pH meter (Beckman Instrument Fullerton, CA 92634, Germany).

Examination of the particles morphology

The morphology of the particles of nanoemulsion produced from aqueous dilution of L-SNEDDS was observed by transmission electron microscope (TEM) (JEM-2000EX II Electron Microscope, JEOL, LTD, Tokyo, Japan). For examination by TEM, 1ml of the preparations were diluted with distilled water to 25 ml and mixed well to form homogenous nanoemulsion. A drop of the produced nanoemulsion was placed on a copper grid coated with carbon film and the excess sample was wiped-out immediately using a filter paper and the grid was air-dried at room temperature before examination by microscope (27).

Characterization of S-SNEDDS

Micromeritic properties

The micromeritic properties of solid formulations were evaluated in terms of angle of repose, Carr's index and Hausner's ratio (28). Measurements were done in triplicates.

Powder x-ray diffraction

Powder X-ray diffraction patterns (PXRD) of piroxicam alone, Aerosil 200, Avicel PH 101, physical mixture (PM) of adsorbents (ratio 1:1) with the corresponding amount of the drug present in S-SNEDDS with 5% HPMC and the selected S-sSNEDDS were recorded at
ambient conditions using X-ray diffractometer (Rigaku Denki, Rint-2500VL, Tokyo, Japan). The experiment was conducted at room temperature using monochromatic Cu/K-alfa radiation (1.542Å) and analyzed between 3 and 50°(20). The voltage and current used were 40 kV and 40 mA, respectively and the chart speed was 10 mm/sec (20).

*Fourier transform infra-red spectroscopy*

Infra-red spectra of piroxicam alone, Aerosil 200, Avicel PH 101, a binary mixture of them, PM of adsorbents (ratio 1:1) with the drug mixed with 5% HPMC and the selected S-sSNEDDS were recorded by potassium bromide (KBr) disc method using Perkin Elmer FT-IR Spectrometer (Thermo fisher scientific, Inc., Waltham, MA, USA) (27). The aim of such study was to illustrate the presence of interactions between the components. Powder sample (about 2 mg) was mixed with 200 mg KBr and grinded into fine powder then compressed into KBr disc using a hydraulic press. Each KBr disc was then scanned over a wave number region of 500–4000 cm⁻¹ and with a resolution of 4 cm⁻¹.

*Tablets Physicochemical Testing*

All tablets were evaluated according to both pharmacopoeial (USP- 34/NF-29) (29) and non-pharmacopoeial tests. These tests include uniformity of weight and thickness, hardness test, friability test, drug content uniformity, disintegration time and dissolution tests.

*In-vitro* drug dissolution study

*In-vitro* dissolution tests of piroxicam alone (10 mg) or from the prepared L-SNEDDS in hard gelatin capsules or tablets (both equivalent to 10 mg drug) were performed using USP basket tablet dissolution tester (Abbotta, USA). The test was performed in 500 ml dissolution medium at different pH values (1.2 and 6.8), 75 rpm and at 37±0.5°C. Aliquots of 5 ml were withdrawn from the dissolution medium at different predetermined time intervals and filtered.
through 0.2µm millipore filter. The withdrawn volume was replaced by 5 ml of fresh dissolution media to maintain a constant volume. After proper dilution, samples were assayed spectrophotometrically at 333 nm for their drug contents. Three runs were carried out for each experiment and the results were calculated as mean ±SD.

Bioavailability studies

The study was conducted on two tested S-sSNEDDS formulations (i.e. F6 and F12) and two control formulations (i.e. pure piroxicam, PP and a commercially available tablet dosage form, CD Feldene® 10 mg, Pfizer Inc. USA).

Eight healthy male volunteers (25-29 years of age and weighing 75-90 kg) participated in this study after signing an informed consent document. All volunteers were active, ambulatory, non-alcoholic, non-smoker adults with irrelevant past medical history. They were asked to stop any medication at least 7 days prior to blood sampling. The study was approved by the scientific research ethical committee of Faculty of Pharmacy, Mansoura University, Egypt (IRB 2016-6). In addition, it was carried out under the supervision of Internal Medicine Department in Specialized Medical Hospital, Mansoura University, Egypt. The study was carried out in a random cross-over manner allowing an interval of 14 days between each administration. The volunteers were asked to fast for 12 hr before and 4 hr after taking the tablets together with 200 ml of water. Three milliliters of venous blood were collected just before taking the tablet and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12 and 24 hr after tablet administration. The blood samples were centrifuged at 5000 rpm for 5 min; plasma was then separated and frozen at -20°C until being analyzed.

The plasma concentration of piroxicam was determined according to Savaşer et al. (30) method with slight modification using Shimadzu HPLC system (Shimadzu, Kyoto, Japan). The chromatographic system consisting of a pump (LC-20 AD), degasser (DGU-20A5), CBM-20A interface, UV-Vis spectrophotometric detector (SPD-20A UV-Vis detector) and
phenomenex reversed phase column (C-18, 250×4.6 mm; 5µm particle size, USA). The isocratic mobile phase system consisted of a mixture of acetonitrile/methanol/0.04MKH$_2$PO$_4$ at a volume ratio of 4:1:5 with a pH value of 3.8 and a flow rate of 0.9 ml/min. After precipitating the plasma proteins with ZnSO$_4$, MgSO$_4$ and acetonitrile/methanol (3:1), piroxicam was detected at a wavelength of 333 nm.

**Pharmacokinetic parameters**

Pharmacokinetic analysis was performed according to non-compartmental model. The maximum plasma concentration ($C_{\text{max}}$) and the time at which it was attained ($T_{\text{max}}$) were obtained directly from plasma concentration vs. time curve. Also, elimination rate constant ($K_{e}$) and biological half-life time ($T_{\frac{1}{2}}$) were estimated from the terminal linear portion of the plasma concentration-time profile. The area under plasma concentration-time curve ($\text{AUC}_{0-24\text{hr}}$) was calculated by using trapezoidal rule. In addition, AUC extrapolated to infinity ($\text{AUC}_{0-\infty}$) was calculated from $\text{AUC}_{0-24\text{hr}}$ by addition of the value ($C_{\text{last}}/K_{e}$), where $C_{\text{last}}$ is the plasma concentration measured at the last time point. Percentage relative bioavailability ($\%F$) is the ratio between $\text{AUC}_{0-\infty}$ of the tested formulations (F6 and F12) to that of pure drug or Feldene® dispersible tablet.

**Statistical analysis**

All the data was expressed as mean ± SD and statistical analysis was performed by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test using Graphpad Prism Software (version 5.00; GraphPad Software, San Diego, CA, USA).
Results and discussion

Solubility studies

Self-emulsifying formulations should be clear monophasic liquids at room temperature when introduced to aqueous phase to allow the availability of the drug in solution. Therefore, identifying the oil, surfactant and co-surfactant that has the maximum drug solubility is very important to achieve optimum drug loading (31). Screening of piroxicam solubility proved that coconut oil (medium chain triglyceride) and soybean oil (long chain triglyceride) possessed the highest solubility values as a result; they were selected as oil phases for SNEDDS formulations. In addition, the solubility was tested in different surfactants, co-surfactants and cosolvents and their maximum value was obtained with Tween 80 as a surfactant, Transcutol HP as a co-surfactant and PEG 400 as a cosolvent (Figure 1).

Tween 80 (HLB 15) is non-ionic, non-toxic and biocompatible surfactant that is less affected by the change in pH and ionic strength throughout GIT. Transcutol HP (HLB 4) is used as a co-surfactant that aided the surfactant to form a more stable interfacial film. It also promoted drug loading into the L-SNEDDS, improved spontaneous emulsification process and fine emulsion formation upon mixing with water (26). Moreover, combination of surfactant and co-surfactant with high and low HLB values resulted in rapid formation of stable emulsion with fine globule size upon dispersion in water (27).

The higher solubility of piroxicam in PEG 400 compared with propylene glycol as a non-volatile solvent may be due to the longer non-polar chain of PEG 400 which reflects hydrophobic interactions of the drug with the liquid vehicle molecule (32).

Construction of pseudo-ternary phase diagrams

Pseudo-ternary phase diagrams were constructed in absence of piroxicam to identify the self-emulsifying regions and SNEDDS formulations. Among the used different S/CoS ratios, the
maximum area of nanoemulsion region was obtained with the ratio 10:1 (Figure 2). Nevertheless, S/CoS ratios of 1:1, 1:2, 2:1, 3:1 and 4:1 gave turbid or course emulsion. Thus, coconut or soybean oil-Tween 80-Trasncutol HP (12/80/8%w/w) were chosen as the optimized L-SNEDDS formulation for further study. The selection of this formula is based on the smallest particle size and the highest stability of the produced nanoemulsion upon its aqueous dilution. These excellent properties may be due to two factors; the first one is the low ratio of oil and the high ratio of surfactant/co-surfactant. The second factor is the higher HLB value of Tween 80 and the solubilizing effect exerted by Transcutol HP (27,33). No significant difference was found in self-emulsifying performance when compared to the corresponding SNEDDS formulations containing 4%w/w of piroxicam.

Self-emulsifying properties are conferred upon a formulation by proper selection as well as the optimum ratio concentrations of lipid and surfactant pair (34,35). In addition, the use of surfactant blends to accomplish the required HLB value for emulsification has been proven to provide superior self-emulsifying properties relative to the use of a single surfactant possessing the desired HLB (36).

**Evaluation of L-SNEDDS**

*Thermodynamic stability study*

The diluted L-SNEDDS yielded clear translucent nanoemulsions within 60 sec without any signs of phase separation or drug precipitation which indicated their robustness to dilution. Thermodynamic stability study was designed to exclude the metastable SNEDDS. It was found that all piroxicam-loaded SNEDDS were stable and did not show any signs of drug precipitation or phase separation.

*Emulsion droplet size, zeta potential and pH measurements*
The droplet size of the emulsion is the crucial factor in self-emulsification performance because it determines the rate, extent of drug release, as well as its absorption (26). The importance of the emulsion droplet size for drug release and bioavailability could be explained by its relation with the surface area. It is well known that, the smaller the droplet size, the higher the surface area available for drug release and exposure to pancreatic lipase which hydrolyzes the oils and forms mixed micelles that promotes drug solubilization and absorption (37). Droplet sizes of the emulsions produced upon dilution of the prepared L-SNEDDS and L-sSNEDDS were found to be 30.0-93.8 nm and 26.9-82.3 nm, respectively with PDI < 0.3 (Table 2). These results indicated that the droplets sizes of nanoemulsion fall in the nano-size range with uniform distribution. The obtained data showed that, the carbon chain lengths of oil, surfactant and their degree of unsaturation have a direct effect on the droplets sizes and the stability of formed emulsion (27). For example, the mean droplet size of diluted F7 and F10 (32.4 ± 5.4 nm, 30.0 ± 4.4 nm, respectively) were significantly smaller than that of F1 and F4 (85.8 ± 11.6 nm, 93.8 ± 6.6 nm, respectively) (ρ<0.05) due to the presence of coconut oil which has a relatively shorter triglyceride chain than soybean oil (23). Also, it was found that the mean droplet size of diluted L-sSNEDDS was smaller than that of diluted L-SNEDDS; this may be due the presence of HPMC-E15 that physically hindered the coalescence of oil globules (38). The droplet sizes of F1, F4, F7 and F10 without incorporation of the drug were found to be 76.43±8.65, 81.70±5.81, 28.01±3.44 and 25.56±2.24, respectively. Droplet size experiments depicted that incorporation of piroxicam in SNEDDS did not have any impact on droplet size (ρ>0.05) nor precipitated after dilution when its concentration was up to 4% w/w.

Regarding zeta potential values of the produced emulsions, they were found to be in the range of -13.30 to -16.11 mV. Hernández and Goymann (39) reported that the zeta potential values above 8-9 mV are required for nanoparticles stability, but 30 mV values are needed for
absolute electrostatic stabilization. The occurrence of negative zeta potential may be due to the anionic groups of the fatty acids and glycols present in oils, surfactants and co-surfactants. The stability of nanoemulsions is irrespective of its surface charge, but it is directly related to the magnitude of the surface charge (21). The pH values of piroxicam L-SNEDDS as well as L-sSNEDDS formulations were varying from 5.54±0.08 to 6.06±0.05 (Table 2).

*Transmission electron microscopy examination*

Transmission electron microscopic images (Figure 3) illustrated that the globules of emulsions produced from dilution of L-SNEDDS are of spherical and homogenous with small size in the range of <100 nm which is consistent with the distribution data (Table 2) obtained from particle size measurement (40).

**Characterization of S-SNEDDS**

*Micromeritic properties*

Table 3 clarified that S-SNEDDS and S-sSNEDDS have a good flow property, being with an acceptable Carr's index (15.54-22.92%), Hausner's ratio (1.18-1.30) and angle of repose (29.74-33.69°). The results for Carr's index and Hausner's ratio were found to be in good agreement with each other. From these results, it can be concluded that solid SNEDDS displayed a good flow characteristics and compression properties which helped in producing tablets with good cohesive properties and content uniformity (28).

*Powder x-ray diffraction (PXRD)*

The PXRD patterns of piroxicam alone, Aerosil 200, Avicel PH 101, physical mixture (PM) and S-sSNEDDS are illustrated in Figure 4. The diffraction spectrum of piroxicam alone showed that the drug is highly crystalline powder that possessed sharp peaks at 2θ values of 8.6°, 14.4°, 17.7°, 21.7° and 27.2°. The PXRD of piroxicam physical mixture and the selected
carriers in a ratio of (1:1) showed the prominent crystalline peaks of both drug and carriers (Figure 4 (d)) indicating the presence of crystalline objects. Silicon dioxide was found to be amorphous as indicated by the absence of diffraction peaks. Powder X-ray diffraction of SNEDDS showed only two broad peaks that correspond to the diffraction pattern of Avicel alone, while the characteristic peaks of piroxicam is completely disappeared. These findings indicated that the drug is either completely dissolved or molecularly dispersed in an amorphous state in the proximity of lipid excipients. These results found an agreement with the literature (20,41).

Fourier transform infrared spectroscopic studies

The result of the infra-red (IR) spectra (Figure 5) showed that pure piroxicam (Figure 5 (a)) exhibits characteristic absorption peaks at 3337, 2930, 1630, 1528, 1434, 1351, 1301, 1182, 773, 622 and 561 cm\(^{-1}\). Whereas, Aerosil 200 (Figure 5 (b)) showed broad absorption peaks at 3424, 1629, 1106, and 808 cm\(^{-1}\). There was no significant difference observed in wave number (cm\(^{-1}\)) or functional group of piroxicam in binary mixtures spectra (figure 5(d-e)) indicating the compatibility of the drug with the adsorbents. Whereas, disappearance of the characteristic absorption band of piroxicam (3337 cm\(^{-1}\)) was observed in all S-SNEDDS spectra (Figure 5 (h-k)). It may be attributed to hydrogen bond interaction between the drug and SNEDDS components, which reflected the enhancement of drug dissolution (41).

Evaluation of tablets

The tablets were evaluated for different physical parameters such as hardness, friability, drug content, disintegration and dissolution. All tablets maintained their hardness in the range of 3.5 to 4.5 kg/cm\(^2\). The result of weight variation test, diameter and thickness of all the prepared tablets were satisfactory as indicated by low coefficient of variation (less than 2%) as shown in Table 4. The loss in total weight of the tablets due to friability was in the range of...
0.019 to 0.243%. Disintegration time for all formulations lies in the range of 7.08 to 8.46 min. The drug content in different formulations was quite consistent and within range (96.07% to 101.46%). All the formulations were found to be within the specification limits (29).

**In vitro dissolution study**

In *vivo* drug dissolution is the rate-controlling step regardless absorption of class II drugs. In spite of the fact that the stomach could discharge HCl at pH 1, this pH of the gastric substance will increase (>3) after food and fluctuate among 1-7 under fasting conditions. As a result, the *in vitro* dissolution of piroxicam SNEDDS was estimated at different pH values (1.2 and 6.8) (42). Statistical analysis was performed for all formulations by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test at the level of $p < 0.05$ (data not shown). Data shown was only for CL vs all SNEDDS formulations, F1 vs F7 and F4 vs F10, F1 vs F4 and F7 vs F10, SNEDDS tablets vs SNEDDS capsules.

Figure 6 showed that the percentage amount of piroxicam released from capsules or tablets containing different SNEDDS were significantly higher than those released from the control capsules (CL) ($p < 0.001$) containing piroxicam alone at all studied pH values.. In conventional SNEDDS, the amount of free energy needed to form emulsion is too low, which allows spontaneous emulsification and resulting in smaller particle size as well as higher drug release rate (43).

The release results illustrated in Figure 6A revealed that, there are many factors affecting piroxicam release from different L-SNEDDS including: pH of dissolution medium, formulation viscosity, particle size of the produced emulsion and the presence of co-solvent. Regarding the pH of dissolution medium, it was found that the higher the pH, the higher the drug release rate. This may be attributed to the relatively higher solubility of piroxicam at higher pH (44). Regarding the formulations viscosity, it was found that formulations with
lower viscosity have higher release rate and vice versa ($\rho < 0.001$). Since soybean oil consists mainly of long chain triglycerides while coconut oil consists mainly of medium chain triglycerides, so soybean oil is more viscous than coconut oil (34). As our results showed the formulations that contained soybean oil possessed higher viscosity and so lower release rate than formulations which contained coconut oil. The effect of viscosity on the release rate may be explained as follows, the higher viscosity may hinder a spontaneous emulsification process and the rate of SNEDDS spreading in aqueous media and resulting in a relatively larger particle size which impeded the diffusion path of the drug through the emulsion globules and so decreased the drug release (34). Also, the particle size of the produced emulsion greatly affects the drug release rate. It is well known that the smaller the particle size, the higher the surface area available for drug release and so the higher drug release. Thus, formulations with smaller particles (F7 and F10) possessed higher release rate ($\rho < 0.001$).

The result also showed that F4 and F10 have higher release rates ($\rho < 0.05$) than F1 and F7, respectively. This may be due to the presence of co-solvents (i.e. PEG 400) which improved piroxicam solubility and so its release rate (15).

Data plotted in Figure 6B, illustrated the dissolution profiles of solid (S-SNEDDS and S-sSNEDDS) formulations. Unfortunately, Aerosil 200 tablets possessed poor tensile strength which broke or laminated at high pressure and even stuck to the punches. In addition, formulations of Aerosil 200 were also very difficult to handle due to their low bulk density ($< 0.05$g/cc) and their tendency to form aggregates (45). Avicel PH 101 is used as an excipient in S-SNEDDS to improve the tableting ability of Aerosil 200 by increasing its density which may decrease due to the presence of adsorbed lipids and surfactants (45). In order to ensure a better and complete drug release from the tablets, 10% croscarmellose sodium (Ac-Di-Sol) were added before compression as a disintegrant (46).
As shown in Figure 6, the SNEDDS tablets showed faster drug release than both SNEDDS capsules and the drug alone (CL) (approximately 1.4-, 6-fold at pH 1.2 and 1.3-, 2-fold at pH 6.8, respectively) (ρ< 0.001). This finding could be primarily attributed to the effects of tablet components particularly crosscarmelose on enhancing water absorption into the tablets, in addition to the role of fine solid components of the tablet formulations as an auxiliary emulsifying agent and emulsion stabilizer (47). For example, Aerosil 200 is a non-porous hydrophilic form of silica that greatly improved the drug dissolution rate from S-SNEDDS by allowing the spontaneous emulsification process (48). In addition to the presence of PPI (i.e. HPMC-E15) in the S-sSNEDDS formulations which maintained a temporarily supersaturated state and apparent higher drug concentration. Also, this effect may be due to adsorption of hydrophobic HPMC chain onto the molecular surface of the drug to form a mechanical barrier that prevent nucleation as well as crystal growth that inhibited drug precipitation (49). In addition to the reduction of the surfactant amount in the formulation, thereby achieving an improved tox/safety profile of the formulation (50). The use of lipids in SNEDDS as drug carriers is thought to enhance the oral absorption via intrinsic lipid pathways. Also, they could reduce the severity of some side effects associated with the long term use of NSAIDs such as GIT ulceration and bleeding (51). So, it could be concluded that S-sSNEDDS may be advantageous to harvest maximum benefit of the SNEDDS.

**Pharmacokinetic study**

The linearity range of the used HPLC method was 0.02–5.0µg/ml with a correlation coefficient (r²) value of 0.9965. The mean piroxicam plasma concentration time profiles are shown in Figure 7. While, the corresponding pharmacokinetic parameters are illustrated in Table 5. The two tested S-sSNEDDS formulations (F6; F12) were selected on the basis of their good release profiles at different pH values and acceptable flow properties of solid SNEDDS.
The results are clearly depicted that a significant increase in AUC$_{0-24h}$ was observed in case of S-sSNEDDS (F12) when compared to the pure drug or F6 ($\rho < 0.001$), but non-significant increase was noted when compared to the commercial formulation Feldene® ($\rho > 0.05$). The $C_{\text{max}}$ of F12 was found to be significantly higher ($\rho < 0.001$) than that of the pure drug, F6 and Feldene®. Also, the $T_{\text{max}}$ was found to be significantly shorter in the case of F12 when compared to the pure drug or Feldene® ($\rho < 0.001$). However, non-significant difference was observed between $T_{\text{max}}$ of both F12 and F6. The decrease in $T_{\text{max}}$ was consistent with the differences in the in-vitro release pattern of different groups. This may be contributed to the marked increase in the absorption rate of piroxicam due to the increased rate of dissolution from S-sSNEDDS than the pure drug. Also, this improvement in bioavailability may be explained by the spontaneous dispersion of S-sSNEDDS in the GI fluid to form a nanoemulsion, where the active components are present in a solubilized state (i.e. free molecule incorporated into the micelles or nanoemulsion droplets) (20). Moreover, the better pharmacokinetic parameters that were observed with F12 in comparison with F6 might be due to the small droplet size that form a large surface area needed for enhanced drug absorption (Table 2). The obtained results also depicted that the favored absorption of piroxicam from F12 formulation was due to the presence of the medium chain triglycerides in coconut oil which enhances lipoprotein synthesis and subsequent lymphatic absorption (52). Earlier reports suggest that the majority of the lipid based systems comprising the long and medium chain fatty acids gain admittance to intestinal lymph and bypass the portal circulation, whereas a larger portion of shorter chain lipids get absorbed into the systemic circulation (53).

Consequently, pure piroxicam preparations and its commercial product are not recommended for analgesia due to their delayed onset of pain relief. But, S-sSNEDDS (F12)
will provide rapid onset of therapeutic effect than PP and CD, which is very important in case of various painful conditions where a fast analgesic effect is required.

**Conclusion**

New self-nanoemulsifying drug delivery system (SNEDDS) is a promising strategy for enhancing the dissolution rate as well as the oral bioavailability of piroxicam. The incorporation of HPMC-E15 into liquid SNEDDS and its conversion into solid dosage form effectively inhibit drug precipitation and offer an additional alternative in the pursuit of improving the product design, manufacture, performance and viability. In addition, it has the advantage of rapid drug dissolution, easy preparation and usage of non-toxic excipients. **Furthermore, in vivo** pharmacokinetic studies showed that S-sSNEDDS has improved the oral bioavailability of the drug which may be due to the collective mechanism of nanoemulsion dispersion with larger surface area. Thus, the developed novel formulation (S-sSNEDDS) would be advantageous in regards to the rapid onset of action, especially in painful conditions where an acute analgesic effect is required.

**Acknowledgments**

The authors would like to express their gratitude to the following pharmaceutical companies for providing us with the gift samples that helped us in our research: Piroxicam sample from Medical Union Pharmaceuticals (MUP) Co., Egypt, Transcutol HP and Labrasol samples from Gattefoseé Co. (Saint-Priest Cedex, France) and cremophor® RH40 and cremophor® EL samples from BASF Corp. (Ludwigshafen, Germany).

**Declaration of interest**

The authors report no declarations of interest.
Appendices

<table>
<thead>
<tr>
<th>Volunteer no.</th>
<th>Initials</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (Kg)</th>
</tr>
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<td>167</td>
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<td>male</td>
<td>25</td>
<td>164</td>
<td>85</td>
</tr>
</tbody>
</table>

References


50. Gao P, Morozowich W. Design and development of supersaturatable self-emulsifying drug delivery systems for enhancing the gastrointestinal absorption of poorly soluble


Table 1. Composition of piroxicam loaded self-nanoemulsifying drug delivery systems (SNEDDS).

<table>
<thead>
<tr>
<th>Ingredients (% w/w)</th>
<th>Formulation Code&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>4</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>8</td>
</tr>
<tr>
<td>Coconut oil</td>
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</tr>
<tr>
<td>Tween 80</td>
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</tr>
<tr>
<td>PEG 400</td>
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<tr>
<td>Transcutol HP</td>
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</table>

<table>
<thead>
<tr>
<th>Ingredients (% w/w)</th>
<th>F2</th>
<th>F3</th>
<th>F5</th>
<th>F6</th>
<th>F8</th>
<th>F9</th>
<th>F11</th>
<th>F12</th>
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<tr>
<td>L-SNEDDS</td>
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<td>35</td>
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<tr>
<td>HPMC</td>
<td>-</td>
<td>5</td>
<td>-</td>
<td>5</td>
<td>-</td>
<td>5</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
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<td>10</td>
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<td>10</td>
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<sup>a</sup> F2-F3, F5-F6, F8-F9 and F11-12 are solid and solid supersaturatable SNEDDS for F1, F4, F7 and F10 liquid SNEDDS, respectively.
Table 2. Emulsion droplet size, zeta potential and pH of L-SNEDDS and L-sSNEDDS

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Particle size (nm)</th>
<th>PDI</th>
<th>Zeta potential (mV)</th>
<th>pH</th>
</tr>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>85.83±11.61</td>
<td>0.29±0.03</td>
<td>-13.30±1.54</td>
<td>5.54 ± 0.08</td>
</tr>
<tr>
<td>F4</td>
<td>93.81±6.65</td>
<td>0.24±0.02</td>
<td>-14.42±2.25</td>
<td>5.78 ± 0.03</td>
</tr>
<tr>
<td>F7</td>
<td>32.44±5.44</td>
<td>0.14±0.01</td>
<td>-15.61±3.51</td>
<td>5.81±0.12</td>
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<tr>
<td>F10</td>
<td>30.00±4.45</td>
<td>0.17±0.05</td>
<td>-15.85±2.95</td>
<td>5.90±0.05</td>
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<tr>
<td>F1(^b)</td>
<td>77.13±6.19</td>
<td>0.24±0.05</td>
<td>-13.53±3.11</td>
<td>5.96±0.10</td>
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<tr>
<td><strong>L-sSNEDDS</strong></td>
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<td></td>
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<tr>
<td>F4(^b)</td>
<td>82.31±12.36</td>
<td>0.30±0.07</td>
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<td>6.06±0.05</td>
</tr>
<tr>
<td>F7(^b)</td>
<td>28.23±6.11</td>
<td>0.17±0.03</td>
<td>-15.86±2.67</td>
<td>6.01±0.07</td>
</tr>
<tr>
<td>F10(^b)</td>
<td>26.92±5.51</td>
<td>0.22±0.01</td>
<td>-16.11±3.25</td>
<td>6.05±0.03</td>
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</tbody>
</table>

L-SNEDDS liquid self-nanoemulsifying drug delivery system
L-sSNEDDS liquid supersaturatable self-nanoemulsifying drug delivery system
PDI polydispersity index
\(^a\) Mean±SD, n=3
\(^b\) formulation code with 5% HPMC
### Table 3. Micromeritic properties of S-SNEDDS and S-sSNEDDS formulations.

<table>
<thead>
<tr>
<th>Code</th>
<th>Property</th>
<th>Bulk density (g/cc)</th>
<th>Tapped density (g/cc)</th>
<th>Angle of repose (θ)</th>
<th>Carr's index (%)</th>
<th>Hausner's ratio</th>
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<tr>
<td>F2</td>
<td></td>
<td>0.37±0.04</td>
<td>0.48±0.11</td>
<td>30.46±2.45</td>
<td>22.92±2.12</td>
<td>1.30±0.30</td>
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<tr>
<td>F3</td>
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<td>0.35±0.06</td>
<td>0.45±0.09</td>
<td>30.10±2.32</td>
<td>20.69±1.19</td>
<td>1.26±0.16</td>
</tr>
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<td>F5</td>
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<td>0.33±0.03</td>
<td>0.40±0.07</td>
<td>29.74±2.24</td>
<td>17.50±1.03</td>
<td>1.21±0.08</td>
</tr>
<tr>
<td>F6</td>
<td></td>
<td>0.32±0.04</td>
<td>0.38±0.05</td>
<td>30.10±1.11</td>
<td>16.27±0.09</td>
<td>1.19±0.01</td>
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<td>F8</td>
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<td>0.32±0.08</td>
<td>0.40±0.10</td>
<td>33.69±1.16</td>
<td>20.00±2.20</td>
<td>1.25±0.17</td>
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<tr>
<td>F9</td>
<td></td>
<td>0.31±0.07</td>
<td>0.38±0.08</td>
<td>32.83±2.32</td>
<td>18.74±1.56</td>
<td>1.23±0.15</td>
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<td>F11</td>
<td></td>
<td>0.29±0.05</td>
<td>0.36±0.04</td>
<td>31.60±1.23</td>
<td>19.44±1.37</td>
<td>1.24±0.14</td>
</tr>
<tr>
<td>F12</td>
<td></td>
<td>0.31±0.02</td>
<td>0.37±0.06</td>
<td>31.22±1.03</td>
<td>15.54±1.83</td>
<td>1.18±0.07</td>
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</table>

S-SNEDDS solid self-nanoemulsifying drug delivery system
S-sSNEDDS solid supersaturatable self-nanoemulsifying drug delivery system

*aMean±SD, n=3
Table 4. Various quality control tests performed for piroxicam SNEDDS tablets.

<table>
<thead>
<tr>
<th>Code</th>
<th>Weight (g) Mean(^a) CV</th>
<th>% Drug content Mean(^b) ±SD</th>
<th>Thickness (mm) Mean(^c) ±SD</th>
<th>Friability(^a) (%) Mean(^d) ±SD</th>
<th>Hardness (Kg/cm(^2)) Mean(^e) ±SD</th>
<th>Disintegration time (min) Mean(^f) ±SD</th>
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<tr>
<td>F2</td>
<td>0.623 0.017</td>
<td>96.1±1.23</td>
<td>5.0±0.30</td>
<td>0.243</td>
<td>3.5±0.62</td>
<td>8.5±0.543</td>
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<tr>
<td>F3</td>
<td>0.713 0.053</td>
<td>96.7±0.81</td>
<td>5.1±0.06</td>
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<td>8.4±0.062</td>
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<td>F5</td>
<td>0.624 0.017</td>
<td>98.5±1.23</td>
<td>5.1±0.03</td>
<td>0.151</td>
<td>3.8±0.32</td>
<td>7.4±0.543</td>
</tr>
<tr>
<td>F6</td>
<td>0.717 0.064</td>
<td>100.8±0.81</td>
<td>5.2±0.03</td>
<td>0.063</td>
<td>4.3±0.13</td>
<td>7.4±0.082</td>
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<tr>
<td>F8</td>
<td>0.630 0.056</td>
<td>97.1±1.39</td>
<td>5.3±0.04</td>
<td>0.132</td>
<td>3.9±0.74</td>
<td>8.1±0.010</td>
</tr>
<tr>
<td>F9</td>
<td>0.715 0.021</td>
<td>96.3±0.51</td>
<td>5.2±0.03</td>
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<td>4.5±0.43</td>
<td>8.0±0.254</td>
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<tr>
<td>F11</td>
<td>0.625 0.033</td>
<td>98.7±0.73</td>
<td>5.3±0.03</td>
<td>0.093</td>
<td>4.1±0.61</td>
<td>7.1±0.831</td>
</tr>
<tr>
<td>F12</td>
<td>0.714 0.063</td>
<td>101.5±0.22</td>
<td>5.2±0.05</td>
<td>0.019</td>
<td>4.4±0.25</td>
<td>7.1±0.352</td>
</tr>
</tbody>
</table>

\(^a\) mean value of twenty determinations  
\(^b\) mean value of five determinations  
\(^c\) mean value of ten determinations  
\(^d\) mean value of twelve determinations  
CV coefficient of variation  
SD standard deviation  
SNEDDS self-nanoemulsifying drug delivery system
Table 5. Pharmacokinetic parameters of piroxicam after oral administration of S-sSNEDDS (F6; F12), CD and PP.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Tested formula&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>0.85± 0.05</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>2.10± 0.45</td>
</tr>
<tr>
<td>$K_e$ (hr&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.05±0.01</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>14.05 ±3.73</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24}$ (µg.hr.ml&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>8.63±0.37</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (µg.hr.ml&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>12.66±0.86</td>
</tr>
<tr>
<td>% $F^b$</td>
<td>______</td>
</tr>
<tr>
<td>% $F^c$</td>
<td>______</td>
</tr>
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</table>

S-sSNEDDS solid supersaturatable self-nanoemulsifying drug delivery system, CD commercial dosage form, PP pure piroxicam

* mean±SD, n=8

$C_{\text{max}}$, peak drug concentration, $T_{\text{max}}$, time to reach the peak concentration, $K_e$, elimination rate constant, $T_{1/2}$, biological half-life, $\text{AUC}_{0-24}$, area under the curve from 0-24hr;

$\text{AUC}_{0-\infty}$, area under the curve from 0-∞, % $F$, percentage relative bioavailability

<sup>b,c</sup> compared to PP, CD respectively

1, 2, 3 indicates PP, CD, F6 respectively.

*<sup>, †, ‡</sup> indicates significant difference at $\rho<0.05$, $\rho<0.01$ and $\rho<0.001$, respectively.
Tables captions:
1. **Table 1.** Composition of piroxicam loaded self-nanoemulsifying drug delivery systems (SNEDDS).

\[ a \] F2-F3, F5-F6, F8-F9 and F11-12 are solid and solid supersaturatable SNEDDS for F1, F4, F7 and F10 liquid SNEDDS, respectively.

2. **Table 2.** Emulsion droplet size, zeta potential and pH of L-SNEDDS and L-sSNEDDS.

L-SNEDDS liquid self-nanoemulsifying drug delivery system

L-sSNEDDS liquid supersaturatable self-nanoemulsifying drug delivery system

PDI polydispersity index

\[ a \] Mean±SD, n=3

3. **Table 3.** Micromeritic properties of S-SNEDDS and S-sSNEDDS formulations.

S-SNEDDS solid self-nanoemulsifying drug delivery system

S-sSNEDDS solid supersaturatable self-nanoemulsifying drug delivery system

4. **Table 4.** Various quality control tests performed for piroxicam SNEDDS tablets.

\[ a \] mean value of twenty determinations

\[ b \] mean value of five determinations

5. **Table 5.** Pharmacokinetic parameters of piroxicam after oral administration of S-sSNEDDS (F6; F12), CD and PP.

S-sSNEDDS solid supersaturatable self-nanoemulsifying drug delivery system, CD commercial dosage form, PP pure piroxicam

\[ a \] mean±SD, n=8

**Figure 1:** Solubility of piroxicam (mg/ml) in various vehicles (oils, surfactants, and co-surfactants; n=3).
$C_{\text{max}}$ peak drug concentration, $T_{\text{max}}$ time to reach the peak concentration, $K_e$ elimination rate constant, $T_{1/2}$ biological half-life, $\text{AUC}_{0-24}$ area under the curve from 0-24hr; $\text{AUC}_{0-\infty}$ area under the curve from 0-$\infty$, % $F$ percentage relative bioavailability.

$b,c$ compared to PP, CD respectively

1, 2, 3 indicates PP, CD, F6 respectively.

*, †, ‡ indicates significant difference at $p<0.05$, $p<0.01$ and $p<0.001$, respectively.
Figure 1. Solubility of piroxicam (mg/ml) in various vehicles (oils, surfactants, and cosurfactants; n=3).
Figure 2. Pseudo-ternary phase diagram with the following components: soybean or coconut (oil), Tween 80 (surfactant), and Transcutol HP (cosurfactant). Gray region represents the microemulsion region. S/CoS ratio was at 5:1 or 10:1.
Figure 3. TEM images of L-SNEDDS formulations (a) F1; (b) F4; (c) F7 and (d) F10.
Figure 4. Powder x-ray diffraction (PXRD) spectra of (a) piroxicam; (b) Aerosil 200; (c) Avicel PH101; (d) physical mixture (PM); (e) F3; (f) F6; (g) F9 and (h) F12.
Figure 5. Fourier transform infrared (FTIR) spectra of (a) piroxicam; (b) Aerosil 200; (c) Avicel PH101; (d) piroxicam with Aerosil 200; (e) piroxicam with Avicel PH 101; (f) Aerosil 200 with Avicel PH101; (g) physical mixture (PM); (h) F3; (i) F6; (j) F9 and (k) F12.
Figure 6. *In vitro* drug dissolution profiles of control drug (CL), different SNEDDS formulations (A) capsules and (B) tablets at pH 1.2 and pH 6.8. Data represents mean ± SD, n=3.
Figure 7. Plasma concentration-time profile of pure piroxicam (PP); commercial dosage form (CD) and S-sSNEDDS (F6; F12) after oral administration in human volunteers.
**Figures captions**

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**Figure 2.** Pseudo-ternary phase diagram with the following components: soybean or coconut (oil), Tween 80 (surfactant), and Transcutol HP (cosurfactant). Gray region represents the microemulsion region. S/CoS ratio was at 5:1 or 10:1.

**Figure 3.** TEM images of L-SNEDDS formulations (a) F1; (b) F4; (c) F7 and (d) F10.

**Figure 4.** Powder x-ray diffraction (PXRD) spectra of (a) piroxicam; (b) Aerosil 200; (c) Avicel PH101; (d) physical mixture (PM); (e) F3; (f) F6; (g) F9 and (h) F12.

**Figure 5.** Fourier transform infrared (FTIR) spectra of (a) piroxicam; (b) Aerosil 200; (c) Avicel PH101; (d) piroxicam with Aerosil 200; (e) piroxicam with Avicel PH101; (f) Aerosil 200 with Avicel PH101; (g) physical mixture (PM); (h) F3; (i) F6; (j) F9 and (k) F12.

**Figure 6.** *In vitro* drug dissolution profiles of control drug (CL), different SNEDDS formulations (A) capsules and (B) tablets at pH 1.2 and pH 6.8. Data represents mean ± SD, n=3.

**Figure 7.** Plasma concentration-time profile of pure piroxicam (PP); commercial dosage form (CD) and S-sSNEDDS (F6; F12) after oral administration in human volunteers.