Formulation and Characterization of Piroxicam as Self-Nano Emulsifying Drug Delivery System

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Abstract

Piroxicam (PIR) is a nonsteroidal anti-inflammatory drug of oxicam category, used in gout, arthritis, as well as other inflammatory conditions (topically and orally). PIR is practically insoluble in water, therefore the aim is preparing and evaluate piroxicam as liquid self-nanoemulsifying drug delivery system to enhance its dispersibility and stability. The dispersibility and stability study have been conducted in Oil, Surfactant and Co-surfactant for choosing the best materials to dissolve piroxicam. The pseudo ternary phase diagrams have been set at 1:1, 2:1, 3:1 as well as 4:1 ratio of surfactants and co-surfactants, also there are 4 formulations were prepared by using various concentrations of transcutol HP, cremophore EL and triacetin oil. All the constructed prepared formulas have been assessed for in vitro drug dissolution, thermodynamic stability, polydispersity index, robustness to dilution, particle size distribution, drug content, and the dispersibility and emulsification time. From the presented research concluded that the self-nanoemulsifying drug delivery system is the convenient method for improving dispersibility and stability of piroxicam.

Keywords: Pseudo-ternary phase diagram, Dissolution rate, SNEDDS, Piroxicam.
Concerning the body, agitation that is needed to form nanoemulsions is made available via the gastrointestinal tract’s digestive motility [4]. SNEDDS works on improving the oral bioavailability related to drugs of poor water solubility via increasing colloidal dispersibility and keeping the drug in dissolved form, in small oil globules, throughout its transit via gastrointestinal tract [2].

Piroxicam can be defined as nonsteroidal anti-inflammatory drug of the oxicam. The majority of NSAIDs actions are inhibiting the prostaglandin synthesis. Piroxicam is effective anti-inflammatory drug used in gout, arthritis, in addition to the other inflammatory conditions (topically and orally) [5, 6]. It is considered to be practically soluble in water, and soluble in anhydrous ethanol as well as methylene chloride. Thus, piroxicam belong to class II with low solubility and high permeability according to BCS parameters [7, 8], so this research aimed to formulate and evaluate piroxicam as liquid SNEDDS for increasing its stability, wettability, solubility in oil and colloidal dispersibility to have convenient delivery of PIR through oral cavity.

**Materials and Methods**

**Materials**

Piroxicam, Transcutol HP, Cremophore EL, and Triacetin oil has been brought from Hyperchem (China). Methanol has been brought from Sigma-Aldrich (Germany). Hydrochloric Acid has been bought from Avantor Performance materials Ind. Netherlands.

**Methods**

**Solubility Studies**

The saturation solubility test was made to select the best solvents for dissolving PIR. PIR's solubility has been evaluated in various co-surfactants, oils and surfactants. Excessive amounts of the PIR powder was added for each vials consisting of (2mL) of chosen vehicle. Following the process of scaling, mixture have been sonicated for five minutes, after that they have been subjected for shaking through the use of water bath shaker at a temperature of (25±1°C) for forty-eight hours. After that, they have been subjected for centrifuging at 3000rpm for twenty minutes, followed by filtration through (0.45μm) membrane filter, and then subjected for dilution with methanol as solvent for dilution of oils, surfactant and co-surfactant, then assayed spectrophotometrically at their respective λ max for their drug contents. Solubility results were calculated as mean ± SD [9, 10].

**Construction of pseudo-ternary phase diagrams**

With regard to hydrophilic-lipophilic balance value as well as the results related to solubility studies, transcutol HP, cremophore EL and triacetin oil have been selected as co-surfactant, surfactant and oil phase, respectively. Through the use of water titration approach, the pseudo-ternary phase diagram has been constructed for determining SNEDDS components’ ratios [11]. Surfactant as well as the co-surfactant (Smix) have been subjected to mixing in various ratios (1:1, 2:1, 3:1 and 4:1). Slow titration of distilled water was added into the Smix:oil mixture under gentle magnetic agitation until a stable, transparent system was created, observation of the transition from transparent to turbid point is noted down. The data gained was subjected to CHEMIX software for construction of ternary plot [12, 13].

**Preparing piroxicam liquid SNEDDS**

Series of liquid SNEDDS formulas were prepared by using triacetin as oil, cremophore EL as a surfactant in addition to using transcutol HP as a co-surfactant in ratios (1:1, 2:1, 3:1 and 4:1), also the oil:Smix ratio (2:8) keep constant as can be seen in (Table 1). PIR was dissolved in oil in screw-capped glass, after that it was mixed with other components as the co-
surfactant, oil phase, respectively. Through the process of scaling, mixture have been sonicated for five minutes, after that they have been subjected for shaking through the use of water bath shaker at a temperature of (25±1 °C) for forty-eight hours. After

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Table 1. Composition of piroxicam liquid SNEDDS (% w/w)

| Formula – code | Smix ratio | Oil: Smix ratio | Triacetin oil % | Cremophore EL, % | Transcutal HP % |
|----------------|------------|----------------|-----------------|-----------------|-----------------
| SNEDDS-1       | 1:1        | 2:8            | 20              | 40              | 40              |
| SNEDDS-2       | 2:1        | 2:8            | 20              | 53.33           | 26.66           |
| SNEDDS-3       | 3:1        | 2:8            | 20              | 60              | 20              |
| SNEDDS-4       | 4:1        | 2:8            | 20              | 64              | 16              |
Evaluations of the prepared piroxicam liquid SNEDDS

Thermodynamic stability studies

The prepared liquids SNEDDS formulations have been subjected for various thermo-dynamic stability tests (centrifugation, heating-cooling cycle and freeze-thaw cycle). Centrifugation was performed at 3500rpm for thirty minutes and inspected for cracking, creaming, phase separation, as well as precipitation, and the stable formulations have been selected for heating-cooling cycle. There are 6 cycles between the refrigerator temperatures 4°C and 45°C with storage at each one of the temperatures for at least forty-eight hours, formulations, which are stable at these temperatures, were subjected to freeze-thaw cycle. There are three freeze-thaw cycles between temperatures of (-21 and +25°C) with storage at each temperature for at least forty-eight hours. The prepared formulations, that were passed thermodynamic stress tests, have been provided for further studies

Droplet size measurement and poly dispersity index (PDI)

All the stable formulations subjected for mean droplet size and polydispersity index (PDI) test by applying 0.5mL of the liquid formula in 250 ml distilled water and gently mixed using magnetic stirrer at 25°C. Droplet size and PDI were measured by using particle size analyzer instrument, a light scattering was monitored at a temperature of 25°C at 90° angle

Robustness to dilution

The prepared formulas of SNEDDS have been diluted to 50, 100, 1000 and 3000-fold with distilled water and 0.1N HCl in 2 separate glass vials. The resultant diluted nanoemulsion formulations have been subjected for shaking and after that visually observed following twenty-four hours for any form of phase separation, coalescence of droplets or drug precipitation

Dispersibility tests and self-nano emulsification time

The effectiveness related to dispersibility and self-nano emulsification time has been evaluated through the use of USP dissolution apparatus II. Each one of the SNEDDS formulation in volume about (0.5mL) has been added to 500 milliliters of the distilled water kept at 37 ± 0.5°C, at 50 rpm for gentle agitation. In vitro efficiency has been visually observed when obtaining transparent homogenous system and for determining time in minutes to reach complete nano-emulsification with the use of grading system, as seen in table 2.

Table 2. Grading system of in vitro performance of the SNEDDS (Dispersibility and self-Nano emulsification time)

| Grade | Time needed for nano-emulsion formation | Appearance |
|-------|----------------------------------------|------------|
| A     | Quickly forming (within one minute) nanoemulsion | Have bluish or clear appearance |
| B     | Quickly forming (within one minute) | A little less clear emulsion, having bluish white appearance |
| C     | Formed within 2min | Fine milky emulsion |
| D     | Slow to emulsify (longer than two min.). | Dull, greyish white emulsion that has a little oily appearance |
| E     | Slow to emulsify (> two min.). | Showing poor or minimum emulsification with large oil globules on the surface |

Determination of drug content

SNEDDS formulation’s drug content has been detected with the use of UV Spectrophotometer assay, 0.4 millilitre (equal to 10 milligram PIR) from each prepared formulation has been diluted to 100 millilitres with methanol and mixed thoroughly. The resultant solutions have been evaluated at estimated \( \lambda_{\text{max}} \) by using UV Spectrophotometer

In vitro dissolution study

The in vitro drug release regarding the pure PIR powder and the prepared SNEDDS formulations were assessed with the use of USP dissolution apparatus-II (paddle type). Paddle type using 0.1N HCl (900mL) as the dissolution media, at 37±0.5°C and 50 rpm, with the use of dialysis bag approach (Molecular cut off 12000 Da) just for the formulas of SNEDDS, and they have been washed with deionized water for the purpose of getting rid of preservatives and then soaked in a dissolution medium (0.1N HCl) overnight to achieve equilibration state. Liquid SNEDDS formula that contain PIR equal to one dose was placed in a dialysis bag, and five milliliters of the dissolution medium has been withdrawn each ten minutes over sixty minutes (10, 20, 30, 40, 50 and 60) and replaced with fresh media (0.1N HCl) in each drawing. The dissolved drug’s amount was evaluated with the use of UV-Spectrophotometer approach at its \( \lambda_{\text{max}} \).

Selection of optimum piroxicam liquid self-nanoemulsion formula

According to the evaluation tests (droplet size measurement and polydispersity index (PDI), in
**vitro** dissolution study and drug content) the best PIR liquid SNEDDS formula was selected.

**Fourier transform infrared spectroscopy (FTIR)**

Infr - red spectra of piroxicam and selected liquid SSNEDDS formula were recorded by using KBr disc approach. The main goal of such study is determining the compatibility and the presence of interactions between components. Powder sample was mixed with KBr and grind into fine powder, after that compressed to KBr disc. All KBr discs has been scanned over wave number region of 400cm⁻¹–4000cm⁻¹ (22).

**Field emission scanning electron microscope (FESEM)**

Morphology of the selected liquid SNEDDS formula has been evaluated with the use of FESEM. Small amount of the nanoemulsion sample was assessed via FESEM (MIRA 3 TESCAN, FRANCE FESEM). The samples were examined at various magnifications which are ranged with instant data capture regarding the images onto personal computers (23).

**Results and Discussion**

**Determination of saturation solubility of piroxicam in different oils, surfactants and co-surfactants**

PIR solubility has been determined in various co-surfactants, surfactants and oils, amongst various oils that have been screened in (Table 3), PIR shows high solubility in triacetin oil. As can be seen in the (Table 4), surfactant cremophore EL and co-surfactant transcutol HP were shown a highest solubility for PIR and therefore, they were chosen for the study.

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

| Surfactant type | Solubility value (mg/mL) mean ±SD* | Co-surfactant type | Solubility value (mg/mL) mean ±SD* |
|-----------------|-----------------------------------|--------------------|-----------------------------------|
| Span 20         | 2.018 ± 0.019                     | Transcutol HP      | 30.9 ± 0.062                      |
| Span 80         | 1.88 ± 0.089                      | PEG 200            | 4.63 ± 0.048                      |
| Tween 20        | 1.28 ± 0.13                       | PEG 400            | 10.59 ± 0.12                      |
| Tween 40        | 0.91 ± 0.086                      | PEG 600            | 2.54 ± 0.023                      |
| Tween 60        | 8.61 ± 0.11                       | Ethylene glycol    | 0.61 ± 0.038                      |
| Tween 80        | 6.17 ± 0.093                      |                    |                                   |
| Cremophore EL   | 33.7 ± 0.054                      |                    |                                   |

*SD standard deviation from mean, n=3

**Pseudo-ternary phase diagram construction**

Pseudo-ternary phase diagrams have been developed for identifying self- emulsifying regions and SNEDDS formulations, pseudo-ternary phase diagram plot for various Smix ratios (cremophore EL: transcutol HP 1:1, 2:1, 3:1 and 4:1) was shown in figures 1. In the pseudo-ternary phase plot, the shaded area performs the area of nanoemulsions while unshaded area performs the area of the emulsion. The plot with a larger shaded area indicates the presence of perfect nano-emulsifying activity of formulated nanoemulsions and beneficial interaction among the Smix, oil and aqueous phase (24).

The oil:Smix 1:9 and 2:8 ratios for all Smix ratios remained as nanoemulsions even upon infinite water titration or dilution, this is possible as cremophore EL with transcutol HP mixture hardly localized on surface regarding nanoemulsion droplets, decreasing interfacial free energy as well as offering mechanical barrier to coalescence causing automatic dispersion. As the ratio of the cremophore EL increase showed best nano-emulsification characteristics indicates the presence...
of perfect nano-emulsifying activity of formulated nanoemulsions. 

Preparation of piroxicam liquid SNEDDS
All the liquid PIR SNEDD formulas that were visually noticed shows yellow and clear mixtures without phase separation or drug precipitation.

Assessment of the prepared liquid SNEDDS

Thermodynamic stability studies
All the prepared formulations of the PIR SNEDDS were passed the thermodynamic stability tests, since there was no indications of drug precipitation or phase separation at end of each cycle. This indicated that formulations are persistent against storage in extreme conditions.

Droplet size measurement and PDI
Droplet size measurement and PDI results are shown in (Table 5). Droplet size of nanoemulsion is very important factor in the self-emulsification performance since it affects the extent and rate of the drug release, in addition to its absorption. That in the small droplet size range, there will be high surface area provided for drug release and absorption. Droplet size related to prepared SNEDDS formulations have been (29.6 nm - 112.7nm), as PDI approximately 0.3 apart from SNEDDS-1 which has been 0.551, PDI lower than 0.3 indicates the optimum uniformity in droplet size distribution following dilution with water.

Table 5. Droplet size measurements and polydispersity index (PDI) of piroxicam liquid self-nano emulsifying systems drug delivery.

| F – code | Mean droplet size (in nm) | polydispersity index (PDI) |
|----------|---------------------------|---------------------------|
| SNEDDS-1 | 112.7                     | 0.551                     |
| SNEDDS-2 | 29.6                      | 0.312                     |
| SNEDDS-3 | 66.7                      | 0.379                     |
| SNEDDS-4 | 41.1                      | 0.262                     |

Robustness to dilution
Dilution is caused by gastrointestinal fluids, also there is no possibility for properly corresponding amount of water for forming nanoemulsion with formulation, robustness to dilution has been carried out with excess of water and 0.1N HCl, also it has been stored for twenty-four hours. All the PIR SNEDDS formulations passed the test and visually observed as clear with no phase separation or precipitation. The capability of SNEDDS formulation for keeping aqueous dilution has been outstanding. It was attributed to the high solubilizing characteristics of excipients, also the ability of forming stable nanoemulsion with small droplet size. This indicate that such formulations have been stable at the infinite water dilution and had high robustness to high dilution.
**Dispersibility tests and self-nano emulsification time**

The emulsification studies have a high importance in estimating the self-emulsifying properties related to the prepared formulations. SNEDDDS must be rapidly and completely dispersed as soon as submitted to the aqueous dilution within mild agitation. The emulsification’s rate is significant important index to determine the emulsification’s effectiveness. All prepared PIR SNEDDDS formulations created nanoemulsion in not more than one minute with grade A and the difference in the self-emulsification times of various formulas in bulk liquid SNEDDDS has been extremely small and due to the fact that observation times have been fast (in seconds), it has been difficult to distinguish between the prepared formulas.

**Drug content**

The drug content of all the prepared PIR SNEDDDS has been more than 96% and there was no considerable difference between different formulations (p > 0.05), which meets the USP requirements and were within an acceptable range (90%–110%) (5), drug content percent of PIR SNEDDDS illustrated in table 6.

### Table 6. The drug content percent of piroxicam liquid self nanoemulsion (mean ±SD) n=3.

| F – code | Drug content % |
|---------|----------------|
| SNEDDS-1 | 99.61 ± 0.078 |
| SNEDDS-2 | 96.82 ± 0.14  |
| SNEDDS-3 | 97.50 ± 0.084 |
| SNEDDS-4 | 98.24 ± 0.061 |

**In vitro dissolution study**

The in vitro drug release profiles regarding F1 to F4 and pure PIR have been assessed in 0.1 N HCl, 50 rpm and 37°C are shown in figure 2. Dialysis membranes were used in this test since it is less susceptible to blockage and the size of the pores are very small. The prepared PIR SNEDDDS formulas showed more than 92 % drug release at end of sixty minutes, yet F4 have higher release 97 %. Since the drug is in dissolved state in SNEDDDS, the release will be faster, the faster release which is due to fine particle size and high surfactant mixture concentrations, that could simply emulsify oil for finer globule.

**Selection of optimum piroxicam liquid self-nanoemulsion**

Liquid SNEDDDS formula F4 was selected as optimum PIR liquid self-nanoemulsion due to the F4 has a higher drug content, higher in vitro release, small droplet size and lower value of PDI.

**Fourier transform infrared spectroscopy**

FTIR is an extremely powerful technique in discovering and evaluating chemical interactions between drug and any excipient and also to control chemical stability. The FTIR spectra of the piroxicam and the selected formula F4 are shown in figure 3, 4 respectively. The main characteristic peak of PIR FTIR was the secondary amine N-H stretching appeared at 3392.17 cm⁻¹.
It had been reported that PIR has two interconvertible crystalline forms, the needle and cubic forms. The IR absorption peaks at 1634 cm$^{-1}$ and 1629 cm$^{-1}$ are assigned to stretching of amide carbonyl groups of the needle form and the cubic form of PIR respectively, peak at 1527.35 cm$^{-1}$ is because of stretching of the second amide band for both crystalline forms of PIR. In this study, the peak at 1637.27 cm$^{-1}$ was found in IR spectrum of PIR, suggesting that the needle form of PIR was used in the present study (37). The PIR spectra also exhibited other characteristic peaks like, C=O stretching of aromatic ring at 1434.78 cm$^{-1}$, C-N stretching at 1351.86 cm$^{-1}$, C-O stretching at 1288.22 cm$^{-1}$, S(=O)2 stretching at 1149.37cm$^{-1}$, -SO2-N stretching at 1033.66 cm$^{-1}$, aromatic CH bending at 825.38 cm$^{-1}$, ortho-disubstituted phenyl at 771.39 cm$^{-1}$ and C-S stretching at 669.18 cm$^{-1}$, which indicate purity of drug (38-40). From the FTIR results, it was found there was no changes in the peaks of PIR spectrum to that of the spectra of the selected formula F4, the results indicate that no chemical interactions have been happened between the PIR and excipients that utilized in the preparation.

Field emission scanning electron microscopic

The liquid SNEDDS F4 was observed under the (FESEM), the results are illustrated in figure 5. The obtained result indicated approximately spherical shape of the droplet.
Conclusion

From this study, a conclusion is made that SNEDDS has provided important dosage form for oral water insoluble drug. SNEDDS that was prepared from triacetin oil, cremophore EL and transcutol HP was important approach for improving stability, wettability, solubility and dissolution rate regarding piroxicam. SNEDDS of piroxicam has been effectively created and evaluated for its in vitro performance. The nano size of such formulations is the cause for improving the drug dissolution because of large surface area provided for drug release and absorption.

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