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RESEARCH ARTICLE

# Meloxicam self-nano-emulsifying drug delivery system with surfactants combination: Formulation and *in vitro* release model

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## Abstract

**Background:** Meloxicam has low water solubility, which affects the dissolution and level of absorption. **Objective:** The study aimed to develop a self-nano-emulsifying drug delivery system (SNEDDS) based on a non-ionic surfactant combination and evaluate the release kinetics model using the DDSolver program. **Methods:** Oil, surfactant, and co-surfactant were selected based on the solubility of meloxicam. **Results:** The best formula showed that 10% of castor oil, 70% of surfactant (tween 80: chromophore RH 40 in 1:1), and 20% of PEG 400 could develop SNEDDS with the 99.84±0.04% percentage of transmittance, 15.47±0.72 sec emulsifying time, and below 50 nm droplet size. The optimised formula is also stable and resistant to various dilutions and pH. The dissolution efficiency (DE0-60) reveals a 5.27-fold increase compared to non-SNEDDS meloxicam. Meloxicam follows Korsmeyer-Peppas release kinetics, while meloxicam SNEDDS follows the Hixon-Crowell model. **Conclusion:** The best formula of SNEDDS consisting of a surfactant combination generate improvement *in vitro* dissolution of meloxicam.

## Introduction

Meloxicam has a low solubility and dissolution rate, limiting the absorption process (Takano *et al.*, 2008) because rapid pain relief requirement in cases of acute and severe pain in rheumatoid arthritis, improvement of dissolution is an essential factor. Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) offer potential advantages for overcoming the low meloxicam solubility, dissolution, and slow initiation of action. The solubility of drugs greatly helps SNEDDS retain drugs in dissolved form in the oil, surfactant, and cosurfactant phases (Kim *et al.*, 2000). Tween 80 is known to provide good emulsification properties (Rocchio *et al.*, 2017). Therefore, it was expected to help nanoemulsion formation after contact with gastrointestinal fluid.

Cremophor can dissolve meloxicam better than Tween 80 (Badran *et al.*, 2014). The combination of Tween 80 and Cremophor RH 40 in the formulation is expected to

synergise in dissolving meloxicam. In addition, it helped the nanoemulsion ordering process and reduced the droplet size. Therefore, this study aimed to develop a nano-emulsifying drug delivery system (SNEDDS) based on a combination of surfactants to increase the solubility and evaluate the release model of *in vitro* dissolution. The DDSolver add-in program in Excel determines meloxicam's release kinetics model from nanoemulsion. A release model described meloxicam releases from SNEDDS filled in hard gelatin capsules.

## Methods

### Material

The tools and materials used in this research were a hot-plate stirrer, centrifuge, dissolution tester, particle size analyser, laboratory equipment, analytical balance, pH meter, meloxicam, Castor oil, Tween 80, Cremophor RH 40, and PEG 400.

### The solubility studies

Meloxicam is determined separately in oil, surfactant, and co-surfactant and is shaken for 72 hours at 37°C. After that, samples were centrifuged at 5000 rpm for 30 minutes, and the supernatant obtained was dissolved in methanol and analysed using a UV-Vis spectrophotometer at  $\lambda_{max}$  (364 nm).

### Pseudo-ternary phase diagram construction

The SNEDDS prototype consisted of a mixture of oil, surfactant, and cosurfactant, with concentrations of each component 10-50%, 20-80%, and 10-30% (Table I).

**Table I: SNEDDS formula**

Formulation	O:Smix	Oil (%)	Surfactant (%)	Cosurfactant (%)
F1	1:9	10	80	10
F2	-	10	70	20
F3	-	10	60	30
F4	2:8	20	70	10
F5	-	20	60	20
F6	-	20	50	30
F7	3:7	30	60	10
F8	-	30	50	20
F9	-	30	40	30
F10	4:6	40	50	10
F11	-	40	40	20
F12	-	40	30	30
F13	5:5	50	40	10
F14	-	50	30	20
F15	-	50	20	30

Description: O = oil; Smix (Surfactant Mixture) = surfactant: cosurfactant

### Preparation of meloxicam SNEDDS

The SNEDDS formulation is carried out by dissolving 7.5 mg of meloxicam in every one ml of SNEDDS components.

### The percentage of transmittance

The transmittance percentage was measured using a UV-Vis spectrophotometer at  $\lambda$  650 nm (Reddy & Sowjanya, 2015).

### Emulsifying time

Emulsifying time was tested visually by pipetting 250 $\mu$ L of SNEDDS into 25mL distilled water at 37°C and stirring at 100 rpm. The time to form a nanoemulsion spontaneously is expressed as the time of emulsification (Reddy & Sowjanya, 2015).

### Accelerated stability study

#### Centrifugation test

The SNEDDS formula was centrifuged at a speed of 5000 rpm within 30 minutes, and the instability of the formulation was observed (Kassem *et al.*, 2016).

#### Heating-cooling cycle test

SNEDDS meloxicam is stored at 4°C and 45°C for at least 24 hours for three cycles. Then the formulation is visually observed for instability, such as phase separation (Kassem *et al.*, 2016).

#### Freeze-thaw test

Meloxicam SNEDDS formulations were stored at -20°C and 25°C for a minimum of 24 hours for three cycles, and the formulations were observed for instability (Kassem *et al.*, 2016).

#### Robustness against dilution

The test was conducted by diluting a SNEDDS formulation into 50x and 1000x using 0.1N HCl, pH of 1.2, phosphate buffer pH of 6.8, and distilled water (Suresh & Sharma, 2011). The percentage of transmittance was measured with a UV-Vis spectrophotometer.

#### Determination of the selected formula

Formula selection was based on the criteria % of transmittance, emulsification time, accelerated stability, and robustness to dilution.

#### Particle size and PDI (poly-dispersibility index)

One ml of SNEDDS meloxicam was added with 250 ml of distilled water and then analysed using PSA (Particle size analyser).

#### In vitro dissolution

The soft gelatin capsules filled the SNEDDS containing 7.5 mg of meloxicam and 7.5 mg of non-SNEDDS meloxicam. The dissolution test *in vitro* was carried out using a basket type on 900 mL phosphate buffer pH 6.8. The device was operated at  $37 \pm 0.5^\circ\text{C}$  with a rotating speed of 100 rpm. The sample was taken as much as 5

mL at five, ten, fifteen, thirty, forty-five, and sixty minutes. The sample absorbance of the sample was measured using a UV-Vis spectrophotometer. The kinetics of the release model was analysed using DDSolver with several mathematical models, such as Higuchi, first order, zero order, Korsmeyer Peppas, and Hixon Crowell (Karthikeyan *et al.*, 2013). The best-fit model is chosen from the highest  $R^2$  and MSC (model selection criterion).

### Data analysis

The results were reported as mean  $\pm$  SD. The dissolution *in vitro* and robustness to dilution between volumes were evaluated using the independent sample t-test. The robustness to dilutions between pH values was analysed using a One Way ANOVA. The experiment results were defined at a 95% confidence level.

## Results

The solubility test ensures the levels of meloxicam that can dissolve in each SNEDDS ingredient (Table II). Using surfactants combination of Cremophor RH 40 and Tween 80 (1:1) gave the highest solubility compared to without the combination. The phase diagram (Figure 1) shows the nanoemulsion zone (red area).

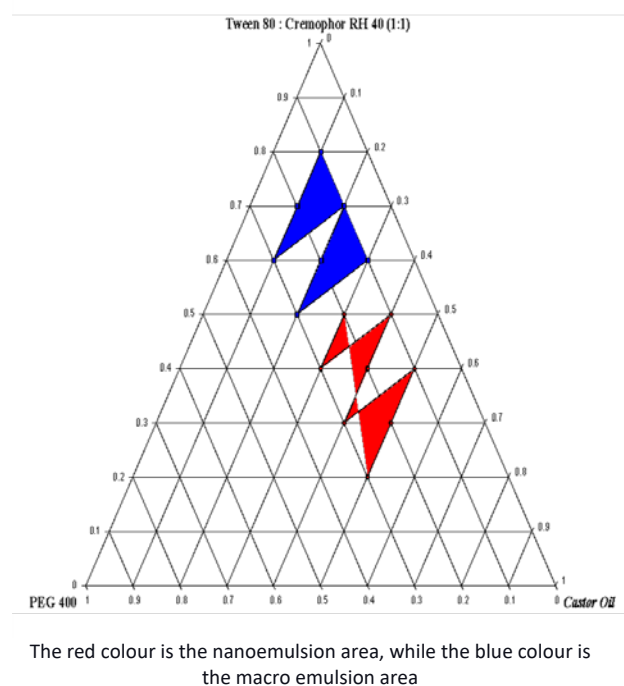
**Table II: Meloxicam solubility data in SNEDDS constituent**

Name of substance	Function	Average meloxicam $\pm$ SD (mg / L)
Castor Oil	Oil	28,400 $\pm$ 0,008
Cremophor RH 40		384,875 $\pm$ 0,013
Tween 80	Surfactant	276,542 $\pm$ 0,003
Cremophor RH 40: Tween 80 (1:1)		390,633 $\pm$ 0,013
PEG 400	Cosurfactant	289,117 $\pm$ 0,007

The area can be utilised to formulate clear pre-concentrate nanoemulsions. The higher the Smix ratio to oil, the more nanoemulsion will be formed quickly, while the increase in oil will form a macroemulsion.

The formula F1-F7 can form nanoemulsions, but only F1-F5 can dissolve meloxicam. The percentage of F1-F5 transmittance close to 100% indicates droplet size in the nanometre range. Among the formula F1-F5, only F4 has an emulsification time greater than one minute. Formula F1 and F2 demonstrate durability in accelerated physical stability tests as indicated by the

percentage transmittance  $p$  value  $>$  0.05. The formulae that meet all the SNEDDS requirements were F1 and F2. However, F2 has a faster emulsification time and lower surfactant concentration. Therefore, F2 was chosen as the best formula, with 17.4 nm in size and a polydispersity index of 0.261, indicating a uniform and homogeneous distribution (Kassem *et al.*, 2016). The Dissolution efficiency (DE0-60) of meloxicam SNEDDS and non-SNEDDS meloxicam were  $64.66 \pm 1.83\%$  and  $12.28 \pm 1.33\%$ , respectively. Hence, SNEDDS increases the DE0-60 by about 5.27 times.



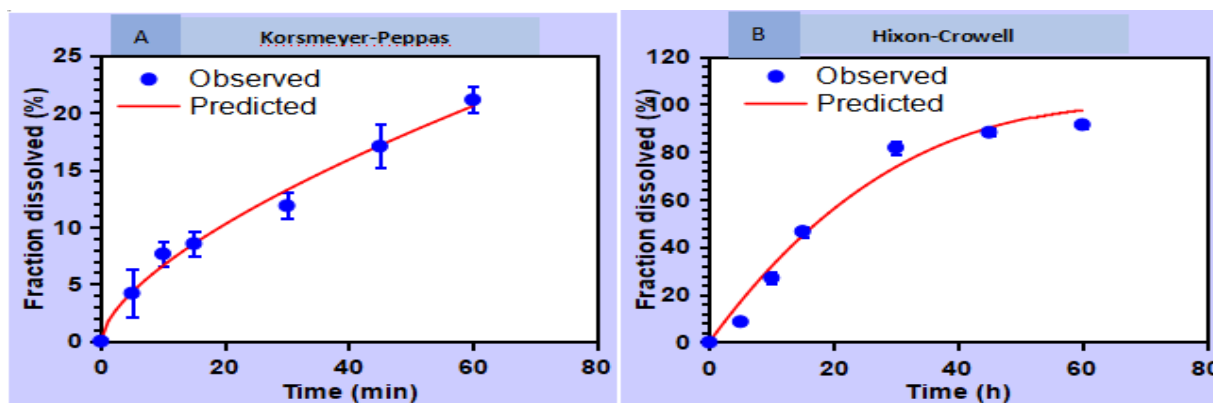
**Figure 1: Triangular area prototype in the pseudoternary diagram**

## Discussion

Tween 80 has a high hydrophilic-lipophilic balance (HLB=15) which could increase the solubility of meloxicam. At the same time, Cremophor RH 40 is a surfactant that can dissolve the highest meloxicam because the lipophilic portion of the hydrogenated castor oil is altered by condensation with polyethylene. The pH of Cremophor RH 40 (six to seven) also increases meloxicam's solubility (Pouton & Pouter, 2008; Taha *et al.*, 2015). PEG 400, as a co-surfactant, dissolve insoluble drug more readily because of a polyoxyethylene-rich environment in the water. Using a Tween 80 and Chromophore RH 40 combination synergises the surfactant layer's quality and localisation in water-oil; hence SNEDDS formula is robust against accelerated stability study.

According to Raval et al. (2012), surfactants can cause unwanted toxicity and gastrointestinal irritation when administered orally with higher concentrations. Therefore, F2 was chosen as this study's best formula for further dissolution study. The F2 formulation has a tiny droplet because of the presence of a surfactant combination. Based on Ren et al. (2009), a mixture of Cremophor RH40 and Tween 80 can provide a

synergistic effect in reducing droplet size so that they can produce a larger surface area for dissolution (Badran *et al.*, 2014). In SNEDDS formulation, meloxicam is in a dissolved form. Hence, it gets released in large amounts than non-SNEDDS meloxicam. *In-vitro* dissolution data of meloxicam show that the most suitable model was the Korsmeyer Peppas with  $R^2 = 0.983$  and  $MSC = 1.85$  (Figure 2).



(A) meloxicam non-SNEDDS; (B) meloxicam SNEDDS

Figure 2: Meloxicam profile of predictive dissolution ( $Q_p$ ) and observative dissolution ( $Q_o$ ) versus time

The value of  $n$  in this model explains the release mechanism of the drug. The value of  $n$  obtained from the equation is 0.643. For the case of cylindrical tablets, the value of  $n$ , which is in the range of  $0.45 < n < 0.89$ , indicates the presence of a non-Fickian transport (Siepmann & Peppas, 2001). Non-Fickian diffusion is characterised by sharp boundaries separating highly swollen areas from dry, glassy ones. It is because meloxicam was filled in a hard gelatin capsule that will form a thick gel when exposed to water. The gel becomes a barrier for the drug to release. On the other hand, SNEDDS meloxicam followed the Hixon Crowell model (Figure 2) with a value of  $R^2 = 0.98$  and  $MSC = 3.18$ . The Hixon Crowell model was also seen in the SNEDDS resveratrol study (Monika *et al.*, 2018).

## Conclusion

The F2 was the best formula, which consisted of ten per cent castor oil, 70% surfactant (tween 80: cremophore RH 40 in 1:1), and 20% PEG 400. The SNEDDS passed all assays and showed higher drug release than meloxicam alone. The release kinetics of meloxicam followed Korsmeyer-Peppas, while Meloxicam SNEDDS followed the Hixon Crowell model.

## Conflict of interest

The authors certify that they have no actual or potential conflicts of interest to declare regarding the subject matter discussed in this manuscript.

## Contributions

All authors contributed to the writing and reviewing of the manuscript. Dr apt. Lina Winarti conceived the ideas and concepts of the project and contributed to the majority of the manuscript writing and revision. Salsabila Ayundiva Putri read, revised, and approved the final version of this submission.

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