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Original Article

MELOXICAM SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM: FORMULATION AND RELEASE KINETICS ANALYSIS

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ABSTRACT

Objective: This study aimed to find the best SNEDDS meloxicam formula and analyze the release kinetics of meloxicam SNEDDS and non-SNEDDS using DDSolver.

Methods: Meloxicam SNEDDS was prepared using sunflower seed oil, Cremophor RH 40 as a surfactant, and polyethylene glycol (PEG) 400 as a co-surfactant.

Results: The best formula obtained subjected to the *in vitro* dissolution study was analyzed using DDSolver. The study shows one selected formula consists of 10% sunflower seed oil, 70% cremophor RH 40, and 20% PEG 400 with a 20.5 nm±12 nm droplet size. The dissolution study showed that SNEDDS could significantly increase the meloxicam release compared to the non-SNEDDS formulation. The kinetics of meloxicam release from SNEDDS formulations follow the Weibull release model (β = 1.00).

Conclusion: This study concludes that SNEDDS best prepared in sunflower seeds oil: Chremophor RH 40: PEG 400 ratio of 1: 7: 2 and has the potency to increase the solubility and dissolution of meloxicam.

Keywords: Meloxicam, SNEDDS, The kinetics of release, DDSolver

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INTRODUCTION

The oral route is the main route of drug delivery for various diseases. Fifty percent of oral administration of drugs is inhibited due to low drug solubility [1], whereas according to the Noyes Whitney equation, drug solubility is directly proportional to the dissolution rate.

Drug dissolution in biological systems is a vital attribute before systemic absorption. *In vitro* drug dissolution study is a relatively fast and inexpensive technique to predict absorption *in vivo* of a drug formulation [2]. The dissolution study can reflect differences in bioavailability due to formulation factors [3]. For drugs with low solubility, appropriate formulation methods are needed to increase their solubility.

Meloxicam is a class II Biopharmaceutical Classification System (BCS) [4], which has very low solubility in water (4.4 g/ml, 25 °C) [5]. This study used a lipid-based drug delivery system, a self-nano emulsifying drug delivery system (SNEDDS), to increase meloxicam solubility. SNEDDS has an advantage in increasing the surface area leading to increased lipophilic drug dissolution and absorption [6].

SNEDDS is an isotropic mixture of drugs, oils, surfactants, and cosurfactants. SNEDDS will spontaneously form a thermodynamically stable oil in water (O/W) emulsion in the presence of light agitation in the gastrointestinal tract [7]. SNEDDS has criteria for particle size (droplet) between 20-200 nm [8]. SNEDDS forms a stable system because it does not contain water; hence, it can be stored more extended than conventional emulsion preparations [9].

Drug solubility is an essential thing in selecting excipients for the SNEDDS formula. In this study, the sunflower seeds oil to use as the oil phase because of its high ability to dissolve meloxicam and its excellent ability to increase lymphatic transport, thus preventing first-pass drug metabolism [10]. Cremophor RH 40 as a surfactant has an HLB of 14-16, which has met the required HLB of oil to dissolve meloxicam well. PEG 400 as a cosurfactant is not toxic or irritative [11].

The previous study improves meloxicam solubility and permeation using ultrafine SNEDDS for transdermal use [12]. Ultrafine SNEDDS meloxicam also increases drug dissolution significantly (up to 70%) in simulated gastric fluid, compared with commercial brands. SNEDDS formulation using sunflower seeds oil as an oil phase, Tween 80 as a surfactant, and PEG 400 as a co-surfactant yielded faster meloxicam dissolution than marketed formulation as well as a pure drug [13]. This research uses cremophor RH 40 as a surfactant because meloxicam is more soluble in cremophor RH 40 than Tween 80.

The literature study showing no other researcher carried out the same study as this research. Therefore, the purpose of this study was to determine the best composition of SNEDDS consisting of sunflower seeds oil, Chremophor RH 40, and PEG 400, as well as to evaluate the release kinetics model using DDSolver. The kinetic release model could explain how meloxicam release from SNEDDS preparations is filled in a hard gelatin capsule.

MATERIALS AND METHODS

Materials

Meloxicam (100,32%) was obtained from Zhejiang Excel Pharmaceutical, Co., Ltd-China. Castor oil or Oleum Ricini was purchased from Samiraschem, Indonesia. Cremophor RH40 from BASF, Germany. Tween 80 from Qingdao sigma chemical co. Ltd, China. PEG 400 and others chemicals were pharmaceutical grades.

Instruments

The instruments used in this study were the USP basket type dissolution test (Logan, Germany), pH meter (Elmetron CP-502, Poland), UV-Vis Spectrophotometer (Genesys 10S, Thermo Scientific, USA), vortex (ThermoFisher Scientific), orbital shaker (ThermoFisher Scientific), centrifuge (EBA 200 Hettich, Germany), analytical balance (Adventurer TM Ohaus, USA), oven (Memmert, Germany), DesignExpert software version 11.0.0, DD Solver program, and glass tools.

Solubility studies

The solubility study was to ensure that the components of SNEDDS were able to dissolve meloxicam. Meloxicam was mixed separately in oil, surfactant, and co-surfactant and kept on shaken for 72 h at 37 °C. The samples were centrifugation at 5000 rpm for 30 min [14]. The

supernatant obtained was dissolved in methanol and analyzed using a UV-Vis spectrophotometer at λmax (361 nm).

Construction of pseudo-ternary phase diagram

SNEDDS prototype consists of a mixture of oil, surfactant, and cosurfactant prepared with a concentration of 10-50%, 20-80%, and 10-30%, respectively seen in table 1. Visual observation can evaluate the ability to form a nanoemulsion system by using a grade A to E grading system [15].

Preparation of meloxicam SNEDDS

Meloxicam SNEDDS are prepared by dissolving the active ingredients in a mixture of oil, surfactants, and co-surfactants. Each formula mixes with a magnetic stirrer on a hotplate (35 °C) to form a homogeneous mixture [16].

Percentage of transmittance

Ten µl SNEDDS mixed with a 10 ml distilled water, and the percent of transmittance measured with a UV-Vis spectrophotometer on λ 650 nm [17].

Emulsifying time

Emulsifying time was tested visually by adding 250 µl SNEDDS into 250 ml distilled water at 37 °C and stirred at 100 pm. The time takes to form a nanoemulsion spontaneously is expressed as emulsifying time [17].

Table 1: SNEDDS prototypes

Formulas	Oil: 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

Note: O = oil; Smix (surfactant mixture) = Surfactants: Cosurfactants

Accelerated physical stability studies

Centrifugation test: The formula was centrifuged at 5000 rpm for 30 min to observe instability [18].

Heating-cooling cycle: The SNEDDS meloxicam formula was stored at 4 °C and 45 °C for a minimum of 24 h for three cycles to observe instability, such as phase separation [18].

Freeze-thaw cycle: The SNEDDS meloxicam was stored at-20 °C and 25 °C for a minimum of 24 h for three cycles to observe the instability [18].

Robustness to dilution: The robustness to dilution test was done by diluting the SNEDDS into 50x and 1000x using HCl 0.1N pH 1.2, phosphate buffer pH 6.8, and distilled water. Then the transmittance was read with a UV-Vis spectrophotometer [19].

Determination of the optimized formula

Optimization of the formula is based on a formula that meets each parameter's criteria, such as a percent (%) transmittance, emulsification time, accelerated stability, and robustness to dilution.

Particle size and PDI (poly dispersibility index)

Liquid SNEDDS (1 ml) was added to 250 ml of distilled water then analyzed using the PSA (particle size analyzer) type DLS (dynamic light scattering). The result of the measurement was average size and polydispersity index [17].

***In vitro* dissolution test**

One ml of SNEDDS containing 7.5 mg meloxicam and 7.5 mg of non-SNEDDS meloxicam fills in a hard gelatin capsule. The capsule is placed in a basket-type dissolution apparatus with 900 ml phosphate buffer pH 6.8 as the medium (37±0.5 °C, 100 rpm). Samples (5 ml) were taken at 5, 10, 15, 30, 45, and 60 min. After each sampling, 5 ml of blank media add to the dissolution flask. The sample was filtered using a 0.45 µm membrane, and the absorbance was measure with a UV-Vis spectrophotometer [20].

Statistical analysis

The data obtained were recorded as mean±SD. Statistically significant differences in experimental results define at 95% confidence level. If the $p<0.05$ was significantly different, whereas if $p>0.05$, the difference was not significant.

RESULTS

Meloxicam was diluted in oils, surfactants, and co-surfactants candidates. The solubility data of meloxicam is seen in table 2.

Table 2: Solubility data of meloxicam in the SNEDDS constituent

Materials	Function	Meloxicam (mg/l)
Castor oil	Oils	28.400±0.008
sunflower seed oil		376.090±0.010
Cremophor RH 40	Surfactants	384.875±0.013
Tween 80		276.542±0.003
PEG 400	Cosurfactants	289.117±0.007

Note: The data was given as mean±SD; n=3, The phase diagram (fig. 1) shows the area of a nanoemulsion. Nanoemulsion seen in blue area, which is wider than the macroemulsion area.

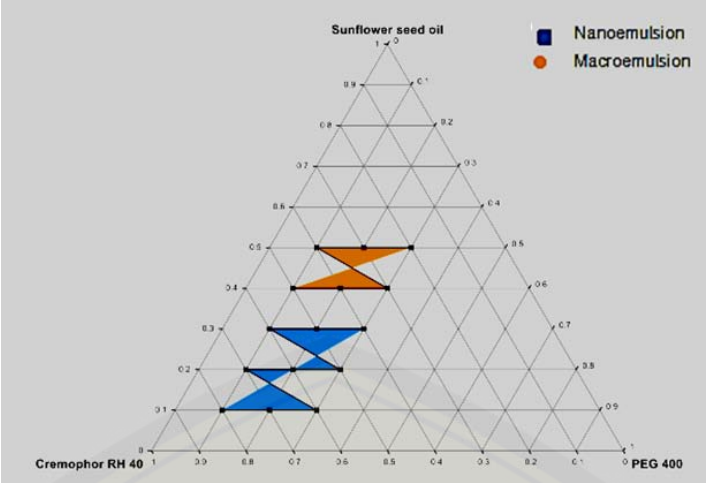

Fig. 1: The SNEDDS prototype area in the pseudoternary diagram

The percentage transmittance and emulsifying time of F1-F6 seen in table 3. The F1-F6 formulations showed survival in the accelerated physical stability tests. However, the study shows that F1 and F2 are the most robust against dilution with volume and pH variations indicated by a p-value>0.05 on the statistical analysis using one-way ANOVA and unpaired t-test.

Table 3: The percentage transmittance and emulsifying time of meloxicam SNEDDS

Formulas	Percentage of transmittance (%)	Emulsifying time (s)
F1	99.91±0.03	163.67±26.54
F2	99.71±0.06	30.00±7.00
F3	99.62±0.04	13.67±1.53
F4	99.46±0.06	251.33±23.46
F5	99.23±0.03	44.00±1.73
F6	98.91±0.03	19.67±2.08

Note: The data was given as mean±SD; n=3, The F2 formula was selected as the best formula. Table 4 showed that F2 metal the criteria.

Table 4: Characteristics of each meloxicam SNEDDS formula

Formulas	Percentage of transmittance	Emulsification time	Thermodynamic stability	Robustness to dilution
F1	√	X	√	√
F2	√	√	√	√
F3	√	√	X	X
F4	√	X	X	X
F5	√	√	X	X
F6	√	√	X	X

Note: √ = Fulfilled; X = Does not meet the criteria

The meloxicam SNEDDS particle size is 20.5±12.0 nm with a PDI of 0.196. The *in vitro* release study shows that the amount of meloxicam SNEDDS released at 60 min was 92.72±1.25%, while for meloxicam non-SNEDDS, it was 21.13±1.12%. SNEDDS formulations of meloxicam exhibited significantly higher dissolution performance as presented by significantly higher % DE60 ($p<0.05$). The release kinetics model analysis shows that the best model is the model with the highest value of R2 adjusted, the smallest AIC [21], and the highest value of the MSC seen in table 5. Based on R^2, AIC, and MSC values, the Weibull model is the best for meloxicam SNEDDS, and Korsmeyer-Peppas is the best model for meloxicam non-SNEDDS.

Table 5: Statistical parameters of meloxicam release model

Dissolution model	Dissolution model parameters					
	Meloxicam non-SNEDDS			Meloxicam SNEDDS		
	R2 adjusted	AIC	MSC	R2 adjusted	AIC	MSC
Zero-order	0.844	22.627	1.529	0.591	48.265	0.561
First-order	0.879	21.104	1.783	0.967	33.110	3.087
Higuchi	0.951	15.720	2.680	0891	40.307	1.887
Korsmeyer-peppas	0.979	11.274	3.421	0.869	42.105	1.588
Hixson-Crowell	0.869	21.620	1.697	0.972	32.221	3.235
Peppas-Sahlin	0.977	12.078	3.287	0.972	33.216	3.069
Weibull	0.978	11.699	3.350	0.981	30.732	3.483

Note: The data was given as mean±SD; n=6

The curve fitting supports the statistical parameter data to get the best release kinetics model. The best model has the distribution of experimental data (Qo) around the predicted dissolution data curve (Qc) as seen in fig. 2 [22].

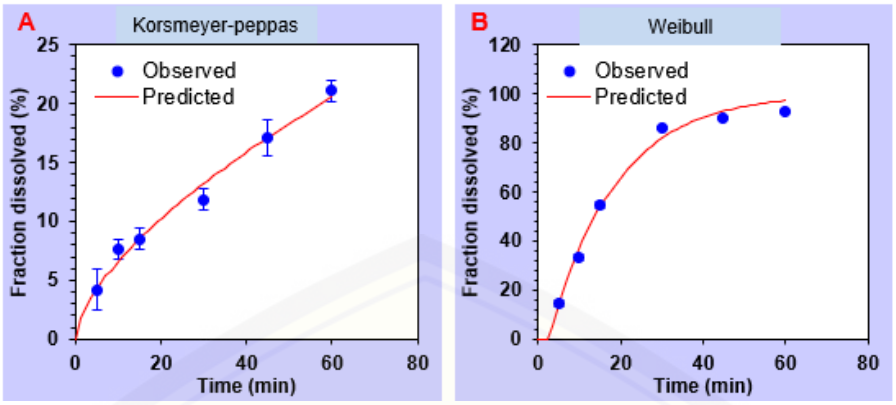

Fig. 2: Meloxicam profile of predictive dissolution (Qp) and observative dissolution (Qo) versus time (n = 6). (A). meloxicam non-SNEDDS; (B). meloxicam SNEDDS

DISCUSSION

The drug-loading capacity of the SNEDDS formulations depends on the solubility of meloxicam in the system. Among the two oils tested, meloxicam has the highest solubility in sunflower seeds oil. Besides, among the two investigated surfactants, meloxicam exhibited higher solubility in Cremophor RH 40. Hydrogenated castor oil's lipophilic moiety condensation with polyethylene makes meloxicam soluble in Cremophor RH 40. Cremophor RH 40 pH value of 6-7 could also enhance meloxicam solubility [20, 23]. The optimal formulation determination is not only by the drug solubility and emulsification efficiency but also by a surfactant synergistic effect; therefore, we select PEG 400 for the SNEDDS formulation. PEG 400 uses as a solvent, co-solvents, and solubilizing in liquid formulations [24]. Therefore many poorly water-soluble drugs are more soluble in PEG 400 because a polyoxyethylene-rich environment is present in water.

The phase diagram shows that the higher Smix will more quickly form a nanoemulsion. However, the higher the oil concentration will create a macroemulsion because high oil concentrations can produce large droplet sizes [25]. Organoleptically, the resulting SNEDDS preparation has a yellow and transparent appearance. F1 to F6 did not experience precipitation and separation between ingredients. In contrast, F7 to F9 experienced precipitation, so not uses for further testing.

The transmittance percentage is use to determine the sample's level of clarity. The percentage transmittance of F1-F6, indicates droplet size in the nanometer range [26]. The higher the oil concentration in the formula, the longer the emulsification time. F1 and F4 are formulas with a high surfactant amount but have longer emulsification time caused by Cremophor RH 40 viscosity, resulting in difficulty disperse [27]. PEG 400, which functions as a co-surfactant, has a vital role in modulating the emulsification time [10]. The higher the concentration of co-surfactants used, the faster the emulsification time.

Accelerated physical stability is essential to differentiate nanoemulsions from emulsions, which will experience phase separation. F1-F6 formulations did not show any phase separation or precipitation during centrifugation and storage in cycling temperature, but only F1 and F2 are the most robust against dilution with volume and pH variations. The nanoemulsion particle size (droplet) is essential for determining the speed and amount of drug dissolved and absorbed in the digestive tract [28]. The meloxicam SNEDDS particle size is 20.5±12.0 nm with a PDI of 0.196. The result indicates the droplet size distribution has high homogeneity or monodisperse [19].

The dissolution study was carried out to compare the release profile of meloxicam non-SNEDDS and a meloxicam SNEDDS. Increasing in dissolution can be seen from the percentage of meloxicam release and DE0-60 (dissolution efficiency). SNEDDS formulations exhibited enhancement in drug dissolution, which is better than a co-grinding technique using hydroxypropyl methylcellulose. The co-grinding technique could only enhance the dissolution of meloxicam by 1.6 folds [29]. The % DE60 calculated from SNEDDS formulations showed 5.11-6.35 folds compared to % DE60 of meloxicam non-SNEDDS. Meloxicam non-SNEDDS DE0-60 was 12.278%±1.331, and for meloxicam, SNEDDS was 68.752%±0.780. The increase in wettability causes high dissolution profiles of SNEDDS meloxicam. Besides, micellar solubilization of drugs in the presence of surfactants [3]. The results support the hypothesis that nano-scale emulsions can improve the release of lipophilic drugs. A previous study of flutamide [30] and quetiapine Fumarate [31] loaded SNEDDS also shows faster and higher dissolution. The SNEDDS formulation could also increase the *in vivo* bioavailability of Felodipine [32].

The statistical parameters showed that Weibull is the best model for meloxicam SNEDDS, while Korsmeyer-Peppas is the best model for meloxicam non-SNEDDS. The curve fitting also shows that meloxicam non-SNEDDS best fit with the Korsmeyer-Peppas curve than others, while meloxicam SNEDDS best fit with the Weibull release curve. The exponent b indicates the mechanism of transport of a drug through the matrix. Meloxicam SNEDDS is having b = 1,00. Hence it shows a combined mechanism (Fickian diffusion and Case II transport). Fickian diffusion denotes drug release that depends on the concentration gradient. In contrast, a case-II anomalous diffusion process is associates with controlled swelling [33]. *Swelling* is an expansion event caused by an increase in volume [34].

Meloxicam non-SNEDDS release from gelatin capsules followed the Korsmeyer-Peppas model with a value of n = 0.637. The value of n (a release exponent) indicates anomalous or non-Fickian drug diffusion, which means the dual-mode of drug release coupling Fickian diffusion and polymer matrix relaxation). The anomalous mode of release of meloxicam non-SNEDDS can cause solvent diffusion to the capsule's interior and induce gelatin relaxation. The excipient composition and the capsule shell influence dispersion and solubilization of the lipid vehicle *in vivo*, influencing the drug release. The capsule shell used for the dissolution study comes from gelatin, which will expand to form a thick gel when exposed to water and then dissolves. The gel formed becomes a barrier to releasing the drug in a burst release.

CONCLUSION

The meloxicam SNEDDS formula consisting of sunflower seed oil, cremophor RH 40, and PEG 400 with a ratio of 1: 7: 2 produced the best SNEDDS characteristics among the other formulas. *In vitro* dissolution release of meloxicam SNEDDS significantly greater than

meloxicam non-SNEDDS. The results show that SNEDDS formulation has the potency to increase the solubility and dissolution of meloxicam.

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AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICT OF INTERESTS

Declared none

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