In Vitro Drug Release Evaluations of Piroxicam Self-Nanoemulsifying Drug Delivery System (SNEDDS)

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ABSTRACT

Introdiction: *Piroxicam is Non-Steroidal Anti-Inflammatory Drug that belongs to the BCS Class 2, characterized by low solubility. The SNEDDS (Self-Nanoemulsifying Drug Delivery System) approach for piroxicam is believed to enhance its solubility and accelerate drug release.* ***Aims***: *This study aims to demonstrate that SNEDDS piroxicam has a faster drug release rate compared to piroxicam powder and commercially available piroxicam capsules.* ***Methods:*** *SNEDDS formulation equivalent to 20 mg of piroxicam, containing a combination of oleic acid, Kolliphor EL, and Transcutol in a ratio of 2:7:4, was tested for drug release using a dissolution method in simulated gastric fluid without enzymes at pH 1.2. The concentration of dissolved drug was measured using a validated spectrophotometric method.* ***Result:*** *At the 45th minute, the dissolution rate of piroxicam SNEDDS reached 101.525%, significantly higher than 47.550% achieved by piroxicam powder and 87,081 % commercially piroxicam capsules at the same time. Additionally, the dissolution efficiency of piroxicam SNEDDS is superior, with a rate of 85.539%, compared to 34.510% for piroxicam powder and 66.17% for commercially available piroxicam capsules.* ***Conclusion:*** *The development of a Self-Nanoemulsifying Drug Delivery System (SNEDDS) for piroxicam has shown promising potential to improve solubility and drug release, as demonstrated by superior in-vitro release rates compared to piroxicam powder and commercial piroxicam capsules*

KEYWORDS: *SNEDDS, piroxicam, in vitro, dissolution, BCS II*

INTRODUCTION

Piroxicam, a nonsteroidal anti-inflammatory drug (NSAID), is categorized as a Biopharmaceutics Classification System (BCS) class 2 compound. It has low water solubility, with a solubility of only 0.023 mg/mL in water. (Kemenkes RI, 2020). One potential approach to improving piroxicam's limitations is to formulate it within a SNEDDS (Self-nanoemulsifying drug delivery system). SNEDDS is an isotropic mixture of oil, surfactant, and co-surfactant that rapidly forms a nanoemulsion dispersion system in a liquid medium. The nanoemulsion droplets produced by SNEDDS range in size from 20 to 200 nm, aiding in active transport across digestive

membranes (Morakul, 2020; Sokkula & Gande, 2020).

In a previous study, the screening of SNEDDS components for piroxicam, including the oil, surfactant, and co-surfactant, was conducted using a fractional factorial design method. The selected components were triacetin as the oil, Cremophor EL as the surfactant, and Transcutol as the co-surfactant. (Nugroho et al., 2023). Dissolution is a key process in drug delivery that governs the release of a drug from its dosage form and its availability for absorption in the body. For a drug to be absorbed into the bloodstream and produce a therapeutic effect, it must first dissolve in the gastrointestinal fluids and exist in a soluble form.

The rate and extent of dissolution are vital for drug efficacy, especially for orally administered drugs. A faster dissolution rate can lead to quicker onset of action, while poor dissolution may result in insufficient drug absorption and reduced therapeutic outcomes(Marroum, 2014). Advanced drug delivery systems, such as SNEDDS, are designed to enhance dissolution by increasing the drug's surface area, improving solubility, and facilitating a more efficient drug release (Shazly & Mohsin, 2015). By optimizing dissolution, these systems aim to improve the bioavailability and overall effectiveness of the drug.

Dissolution is a fundamental aspect of SNEDDS that directly impacts the drug's bioavailability, consistency, and overall

therapeutic performance (Gayathri et al., 2021). Ensuring efficient dissolution through careful formulation and testing is essential for harnessing the full potential of SNEDDS in improving drug delivery and patient outcomes . This study aims to demonstrate that the SNEDDS formulation approach for piroxicam can enhance drug release, as evaluated by the parameters of % dissolution and dissolution efficiency.

MATERIAL AND METHODS

Piroxicam was sourced from PT Zenith Pharmaceutical, while triacetin was obtained from Loba Chemie. Oleic acid, Kolliphor EL, and HCL were supplied by Sigma Aldrich, Transcutol by Gattefossé, and methanol by Smart Lab.

Preparation of SNEDDS Piroxicam

A mixture of oleic acid, Kolliphor EL, and Transcutol in a 2:7:4 ratio, totaling 10 grams, was homogenized at 500 rpm. Piroxicam was gradually introduced to the mixture until precipitation of its powder was observed. Once saturation was achieved, the mixture underwent centrifugation at 10,000 rpm for 120 minutes, and the supernatant was separated. The prepared SNEDDS were kept at room temperature for further analysis (Nugroho et al., 2023).

Validation of Piroxicam Analysis Method

Piroxicam can be analyzed using spectrophotometry because it contains chromophores in its molecular structure that absorb electromagnetic radiation in specific

wavelengths. This method is widely used because it is simple, cost-effective, and provides reliable results for pharmaceutical analysis (Girish et al., 2021; Salim & Rajab, 2020). Validation of piroxicam analysis method involves testing and evaluating various parameters to ensure the accuracy, reliability, and consistency of the method. The analysis validation method based on the International Conference on Harmonization (ICH) guidelines, namely specificity, linearity, accuracy, precision, LOD, and LOQ (Miranda et al., 2021).

Specificity

The test was conducted by comparing the UV spectra of SNEDDS piroxicam with piroxicam standard. SNEDDS piroxicam and piroxicam standard were made at a concentration of 10 ppm using HCl pH 1.2 solvent, the spectrum was seen at a wavelength of 200-400 nm.

Linearity

Piroxicam standard solution was made into standard series 4; 6; 8; 10 and 12 ppm using HCl solvent pH 1.2, the absorbance was measured at the maximum wavelength. The absorption results were then made into a linear regression relationship between concentration (ppm) and absorbance.

Accuracy and *precision*

LOD and LOQ

The limit of detection (LOD) and the limit of quantification (LOQ) are determined using the standard deviation of the response and the slope of the calibration curve regression.

Self-Nanoemulsifying Drug Delivery System

$$LOD = \frac{3\,Sy/x}{b}$$

$$LOQ = \frac{10Sy/x}{b}$$

Characterization of SNEDDS Piroxicam

Drug loading

A 100 µl sample of SNEDDS piroxicam was dissolved in methanol to make a 5 ml solution. From this solution, 1 ml was taken and further diluted with methanol to a total volume of 10 ml. The piroxicam content in the resulting solution was then analyzed using a UV spectrophotometer at a wavelength of 333 nm (Nugroho et al., 2023).

Emulsification time

The emulsification time test involved a 100-fold dilution of SNEDDS using a type II dissolution tester. In this method, 2 ml of SNEDDS was introduced into 200 ml of distilled water (aquadest) kept at a temperature of 37 ± 1°C and stirred at 100 rpm. The time taken to form a uniform nanoemulsion dispersion was recorded (Kuncahyo et al., 2019).

Droplet size

The droplet size of a SNEDDS is often measured after aqueous dispersion via dynamic light scattering (Buya et al., 2020). The droplets in the dispersion scatter the light at different angles depending on their size. Backscatter detection is an optical setup that allows for the measurement of samples with smaller sizes and lower concentrations like SNEDDS piroxicam at a scattering angle of 173° (Knysh et al., 2023). The process entailed
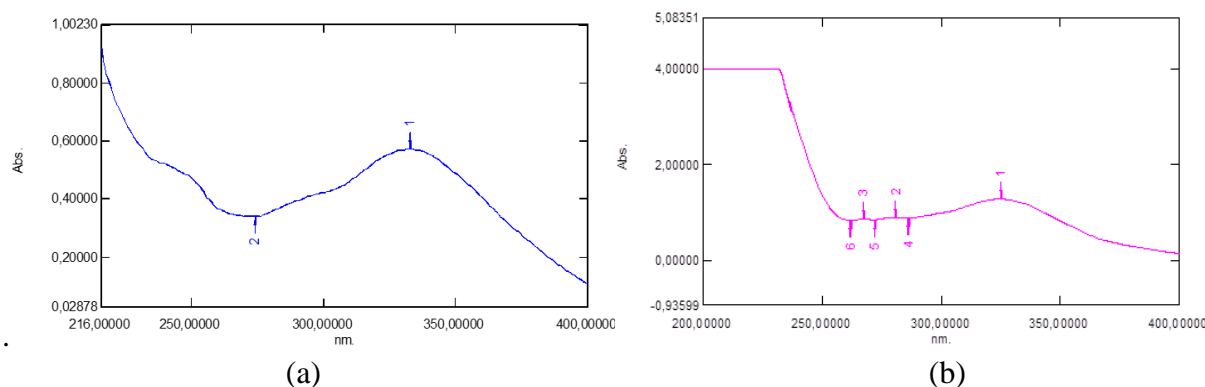
Figure 1. Piroxicam spectrum (a), piroxicam spectrum in SNEDDS components (b).

diluting 0.1 ml of SNEDDS in 10 ml of distilled water, followed by homogenization using a magnetic stirrer to create a nanoemulsion system. The droplet size was then measured at room temperature using a particle size analyzer, configured to a scattering angle of 173° (Nugroho et al., 2023).

Dissolution Test

The tests were conducted by comparing SNEDDS piroxicam equivalent to 20 mg of piroxicam encapsulated in a gelatin capsule, 20 mg of piroxicam powder encapsulated in a gelatin capsule, and commercially available piroxicam capsules. The SNEDDS piroxicam test used a type 1 dissolution apparatus with 900 ml of simulated gastric fluid without enzymes at pH 1.2, at a speed of 50 RPM and a temperature of 37ºC. Samples of 5 ml were taken from the dissolution medium at 5, 15, 30, 45, and 60 minutes, and replaced with fresh dissolution medium. The dissolved content was analyzed using a UV-Vis spectrophotometer at the maximum wavelength. The dissolution test results were based on the percentage of piroxicam dissolved (%Q) over 45 minutes and the

dissolution efficiency (DE) over 60 minutes, compared to pure piroxicam powder and commercially available piroxicam products (Kemenkes RI, 2020).

RESULTS AND DISCUSSION

SNEDDS is a formulation consisting of oils, surfactants, co-surfactants, and active pharmaceutical ingredients that spontaneously forms an oil-in-water (o/w) emulsion upon gentle mixing in an aqueous medium. A mixture of triacetin, Kolliphor EL, and Transcutol in a 2:7:4 ratio exhibits a transparent appearance. A transparent, bluish solution signifies the formation of a nanoemulsion, while a fully clear solution indicates the presence of micelles.

Validation of an analytical method is the process of proving, through laboratory testing, that an analytical method is reliable and provides dependable data for a given procedure. The specificity parameter describes the extent to which a sample can identify a particular analyte within a complex mixture of matrix excipients. From Figure 1, it is shown that the addition of the placebo, which is a component of SNEDDS, does not affect the
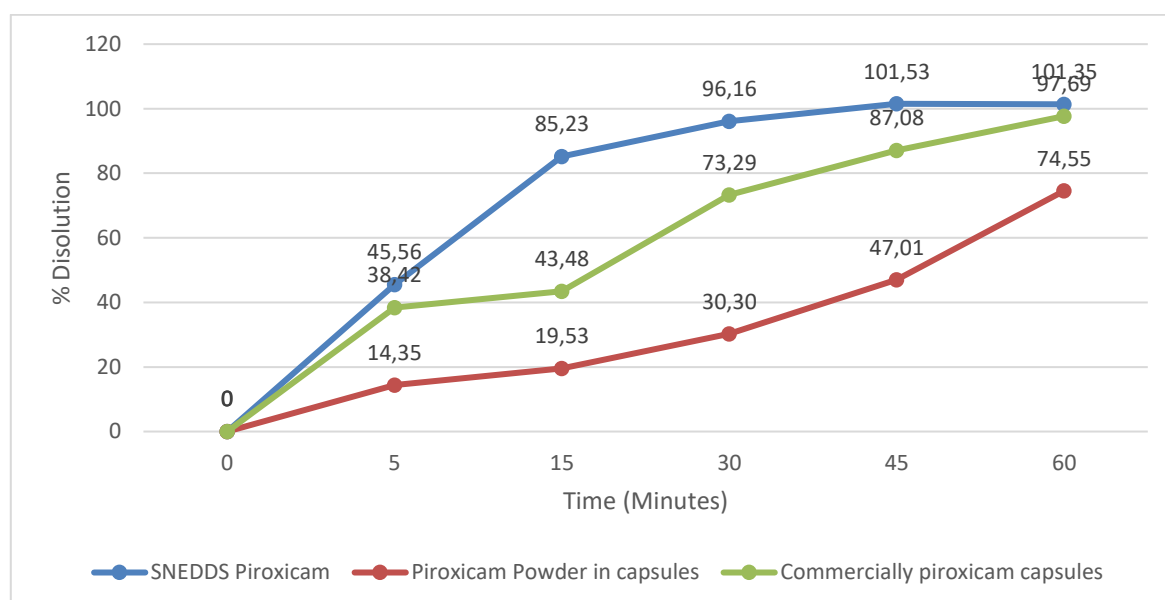
Figure 2. Results dissolution test for piroxicam SNEDDS, piroxicam powder in capsules, and commercially available piroxicam capsules.

absorption of piroxicam at the 333 nm region (Ferraz et al., 2015). For the linearity parameter, the calibration curve equation is y = 0,0714x-0,005 with a correlation coeffcient (r) = 0,9982. The correlation coefficient value in linearity indicates the accuracy of the analytical method if the correlation coefficient is >0.997 (Nisa et al., 2021; Riyanto, 2014).

The characterization of Piroxicam-loaded SNEDDS is presented in Table 1. The formulation demonstrated a drug loading capacity of 72.13 ± 0.69 mg/ml, which reflects the ability of the SNEDDS components to dissolve poorly soluble drugs. Higher drug solubilization capacity translates to a smaller dosage form. Emulsification time represents the speed at which SNEDDS forms

Table 1. Characterization SNEDDS Piroxicam

Characterization	Result ± SD
Drug loading (mg/ml)	72.13±0.69
Droplet size (nm)	12.88±1.43
Emulsification time (s)	14.43±1.54

nanoemulsions in the body, facilitated by peristaltic movements in the digestive tract. A shorter emulsification time suggests faster drug absorption and a quicker onset of therapeutic effects. Additionally, the size of the emulsion droplets plays a pivotal role in SNEDDS development, as it significantly impacts in vitro properties, such as dissolution, and in vivo characteristics including absorption (Rehman et al., 2022). Smaller droplet sizes increase the surface area, potentially improving the drug's solubility and permeability (Buya et al., 2020).

The in vitro dissolution study on SNEDDS will provide an overview of drug release in the gastrointestinal tract by enhancing drug solubility and absorption. This is because the droplet size of SNEDDS influences the rate of drug release, where smaller particle sizes have a larger surface area and facilitate dissolution. In Figure 2 piroxicam SNEDDS enhances the dissolution of piroxicam compared to piroxi-

cam powder. The percentage of piroxicam SNEDDS dissolved at the 45th minute is 101.525%, compared to 47.550% for piroxicam powder and 87,081 % commercially piroxicam capsules at the same time, where the requirement of the Indonesian Pharmacopoeia VI states that at least 75% must dissolve within 45 minutes (Kemenkes RI, 2020). The dissolution efficiency of piroxicam SNEDDS is also higher, at 85.539%, compared to 34.510% for piroxicam powder, and 66,17% for commercially piroxicam capsule Compared to piroxicam powder and commercially available piroxicam capsules, SNEDDS shows potential in enhancing drug release, as evidenced by dissolution testing, where the dissolution rate and dissolution efficiency of piroxicam SNEDDS are superior. In another study, piroxicam SNEDDS using the same SNEDDS components, namely Cremophor EL as surfactant, Transcutol HP as co-surfactant, and Triacetin as oil with different proportions, showed a drug release of 92–97% within 60 minutes (Salim & Rajab, 2020)

The mechanism of drug release in SNEDDS (Self-Nanoemulsifying Drug Delivery Systems) is closely tied to its ability to enhance drug release. SNEDDS work by forming a nanoemulsion in the gastrointestinal tract upon contact with digestive fluids (Abushal et al., 2022). This nanoemulsion consists of nano droplets that significantly increase the surface area available for drug dissolution. The increased surface area, combined with the improved solubility of the drug within the nanoemulsion, leads to a more efficient and rapid release of the drug. The smaller droplet size facilitates the dissolution process, allowing the drug to be absorbed more quickly and effectively in the intestines. This mechanism ultimately enhances the bioavailability of the drug, making SNEDDS a powerful strategy for improving the release and therapeutic effectiveness of poorly soluble drugs (Morakul, 2020).

Dissolution efficiency is an important measure in assessing the effectiveness of drug delivery systems. It indicates the percentage of the drug that dissolves within a defined time period under standardized conditions. Higher dissolution efficiency indicates that a greater amount of the drug becomes available in a dissolved state, which is essential for absorption in the gastrointestinal tract. In the context of advanced drug delivery systems like SNEDDS, dissolution efficiency is often enhanced due to the nano-sized droplets formed upon contact with digestive fluids. These droplets increase the surface area for dissolution and improve the solubility of the drug, leading to more efficient and consistent drug release. A high dissolution efficiency is particularly beneficial for poorly soluble drugs, as it can significantly improve their bioavailability and therapeutic effect.

CONCLUSION

The development SNEDDS (Self-Nanoemulsifying Drug Delivery System) of

piroxicam shows promising potential to enhance the solubility and drug release, as evidenced by better in-vitro drug release tests compared to piroxicam powder in capsules and commercially available piroxicam capsules. Limitation of this research is that in vitro evaluations focus on drug release but may not provide insights into the drug's subsequent absorption, distribution, or metabolism in the body. In the future, the development of SNEDDS in solid form is necessary to facilitate the development of products such as tablets and capsules.

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