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Development, Characterization and Evaluation of Anti-Inflammatory Drug Loaded Snedds for Gout

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ABSTRACT

A hydrophobic and highly permeable medication, celecoxib is classified as class II in the biopharmaceutics categorisation system (BCS). After oral treatment, celecoxib's low water solubility causes significant absorption variability. In order to combat gout, this study sought to create a celecoxib self-nanoemulsifying drug delivery system (SNEDD). Sesame oil, span 80, and PEG 400 were used to create the pseudo-ternary phase diagram that was used to optimise the SNEDDS formulation. Surface response design was utilised to optimise the formulation, and the resultant C-SNEDDs formulation demonstrated a 100% transmittance, a small globule size of 100.5 nm, and high solubility up to 133.6. According to in vitro release experiments, the formulation's celecoxib release was high and quick. In contrast to traditional tablets, the self nanoemulsifying drug delivery system (SNEDDS), which uses celecoxib as a model drug, was found to achieve an effective therapeutic concentration and is intended to reduce the risk of heart attacks by reducing the dosage and relieving pain related to inflammation with a single dose. Zero-order and first-order drug release kinetics were demonstrated by C-SNEDDS in vitro release. With improved solubility, the created formulation was found to be superior to pure celecoxib, indicating that a lipidic system is an effective drug delivery method for treating gout.

Keywords: *Gout, SNEDDS, Anti-inflammatory drug, celecoxib*

1. INTRODUCTION

The most common type of inflammatory arthritis, gout, is brought on by the buildup of monosodium urate (MSU) crystals in the tissues and joints (1). Hyperuricemia is frequently linked to this prevalent metabolic condition (2). An enzyme called xanthine oxidase (XOD), which is essential to gout, catalyses the conversion of hypoxanthine to xanthine and subsequently to uric acid (3). When renal excretion is compromised, the body accumulates uric acid, which causes hyperuricemia and, in turn, the deposition of MSU crystals in the tissues and joints (4). MSU crystals have the ability to stimulate innate immune cells, which leads to the release of proinflammatory cytokines such tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (5). As of right now, corticosteroids or nonsteroidal anti-inflammatory medications (NSAIDs) are the first-line treatments for acute gout (5). The best course of action for treating chronic gout is to use diuretic acid medicines in conjunction with allopurinol, an XOD inhibitor (6).

Celecoxib has a weakly acidic (pKa = 11.1) and hydrophobic (log P = 3.5) nature. It is a white, crystalline powder that is

nearly insoluble in water, which increases the degree of absorption variability following oral administration. It is often taken orally once or twice a day, for a total dosage of 100–200 mg twice a day

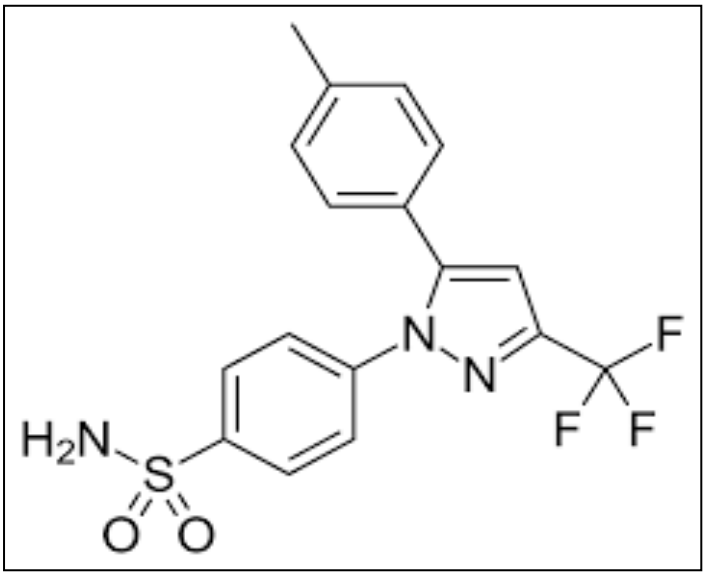

Figure 1: Structure of celecoxib

An SNEDDS is a drug delivery system that, when exposed to aqueous media, including gastrointestinal fluids, forms a thin oil-in-water nano-emulsion using a combination of oils, surfactants, and co-surfactants. The therapeutic efficacy of poorly soluble medications can be increased by increasing their solubility and bioavailability using this thermodynamically stable system (7). One prospective drug delivery method that can improve celecoxib solubility, absorption, and bioavailability is celecoxib self-nano-emulsion drug delivery (C-SNEDDS). The best selection of oils, surfactants, and co-surfactants is necessary for the creation of a C-SNEDDS. (8) Selecting these ingredients is essential to creating a self-nanoemulsifying formulation that is both stable and efficient. Based on information gathered from the literature, the oils, surfactants, and co-surfactants chosen for this investigation were chosen. Because oils are essential to stabilising the emulsion and defining its characteristics, their choice is crucial in SNEDDS. Labrafil, sesame oil, Capryol-90, olive oil, Labrafac, anise oil, almond oil, soybean oil and maize oil were the oils used for this investigation. Because of their reputation as efficient emulsifiers that may create oil-in-water (O/W) emulsions when they come into contact with an aqueous phase, these oils were chosen (9). Each of these oils has distinct properties that can affect the viscosity, stability, and compatibility of the emulsion with different active components (10, 11).

Because they lessen the interfacial tension between the water and oil phases, surfactants are crucial for the stability of emulsions. Hydrophilic non-ionic surfactants such as Cremophor El, Tween 20, Tween 80, Span 20, and Span 80 were used in this investigation. These surfactants were chosen because of their high hydrophilic–lipophilic balance (HLB) values, which show that they can efficiently stabilise O/W emulsions (12–14). Additionally, because safety is a top priority in pharmaceutical and cosmetic applications, their low oral toxicity is essential (15, 16). Co-surfactants are frequently used with surfactants to change the characteristics and increase the stability of an emulsion. Propylene glycol, PEG 400, and transcutol were the co-surfactants chosen for this investigation. These co-surfactants were selected due to their capacity to enhance the overall stability, viscosity, and droplet size distribution of an emulsion. (17) They are appropriate for producing emulsions with certain required properties because of their compatibility with the selected oils and surfactants. (18) The goal of the current study was to create a C-SNEDDS by carefully choosing its oils, surfactants, and co-surfactants. Here, we introduce a brand-new SNEDDS technology that creates a gout nano-emulsion.

2. MATERIALS AND METHODS

Materials: Analytical-grade materials and chemicals were produced and provided from many sources. The supplier of celecoxib was Yucca Enterprises in Mumbai. Research-Lab Fine chem Industries, located in Mumbai, India, was the supplier of span 60, cholesterol, chloroform, methanol, sodium phosphate, sodium hydrogen phosphate, and carbopol 934.

Screening of Components: Celecoxib's equilibrium solubility in a range of oils, cosurfactants, and surfactants was investigated. An SNEDDS was created using oils with varying saturation levels (medium- or long-chain triglycerides) to examine their capacity for solubilisation and nano-emulsification. Because it significantly affects the drug's solubility and absorption, the oil with the highest capacity to solubilise celecoxib was selected. Among the oils that were examined were

sesame oil, olive oil, anise oil, almond oil, soybean oil, maize oil, Labrafil, Capryol-90, and Labrafac. (19) The hydrophilic non-ionic surfactants (Cremophor El, Tween 20, Twen 80, Span 20 and Span 80) that were evaluated had low oral toxicity and high HLB values. The cosurfactants that were evaluated were propylene glycol, PEG 400, and transcutol. Five millilitres of each solvent were mixed with an excess of celecoxib, and the mixtures were stored in closed bottles and vortexed to aid in solubilisation if necessary. For 72 hours, caps were shaken in a water bath set at 37 °C. After centrifuging each mixture for 10 minutes at 15,000 rpm, the mixtures were filtered. After that, samples were diluted 100 times with methanol, and each sample's drug concentration was measured at 254 nm using a UV-VIS double beam spectrophotometer with methanol serving as a blank. (20)

Construction of Pseudo-Ternary Phase Diagram: Celecoxib's maximum solubility in various components led to the selection of PEG 400, Span 80, and sesame oil as the co-surfactant, surfactant, and oil phase, respectively. A pseudo-ternary diagram was constructed using a variety of combinations with different oil, surfactant, and co-surfactant concentrations. The ranges for PEG 400, Span 80, and sesame oil were 10–30% w/w, 20–80% w/w, and 10–70% w/w, respectively. (21) After diluting each mixture 100 times with deionised water, all compositions were visually inspected for the development of nano-emulsions. (56)

Optimization of Formulation: Formulation development has recently made use of experimental design. This approach provides the best results with the fewest experiments and more details on how components affect responses (22). The percentage of each component (PEG 400, Span 80, and sesame oil) was established by pre-optimization study. Software called Design Expert (Version 11.1.2.0) was used to optimise these concentrations. The concentrations of PEG 400, Span 80, and sesame oil were determined to be independent variables or factors. The limitations of each independent variable were determined and recommended in the preceding section based on the pre-optimization study. (23) A formulation is always 100% equal to the total of its parts. The characteristics that were selected were globule size, solubility, and transmittance. The desirability function was used to choose the optimisation batches.

2.1 Characterization of formulations

Drug Content: After dissolving in 10 millilitres of methanol and sonicating for five minutes, the formulations (F1–F15) were identified. Using methanol as the blank, the formulation was appropriately diluted and subjected to UV analysis at 254 nm. (24)

Globule Size, Size Distributions and Zeta Potential: Particle size analysis was performed after the formulations (F1–F15) were diluted with deionised water. On a Malvern Zetasizer (Malvern Instruments, Malvern, UK), dynamic light scattering was used to measure the average particle size, polydispersity index (PDI), and zeta potential. (25)

Dispersibility Studies: Dispersibility studies were used to measure the self-emulsification time. First, using a USP Type II (paddle) dissolution device revolving at 50 rpm at 37 ± 0.5 °C, 1 mL of formulation was introduced dropwise to 100 mL of isotonic phosphate buffer (pH 7.4) while being gently stirred. The self-emulsification process was visually examined. Visual observation of the resulting emulsion during a 24-hour storage period at room temperature was used to measure precipitation. (26)

Transmittance: The C-SNEDDs were reconstituted with distilled water, and any turbidity in the resultant nano-emulsion was visually inspected. Its percent transmittance at 456.5 nm was then measured using a UV-vis spectrophotometer, with distilled water acting as the blank. The tests were conducted after dilution by a factor of 100. (27)

Differential Scanning Calorimetry Studies: A differential scanning calorimeter (DSC) was used to do thermal examination of the optimised C-SNEDDs mixture, as well as of Sesame oil, Span 80, PEG 400, and C-SNEDDs. At a scanning rate of 10 °C/min, the study was carried out in the 50–200 °C range. The reference was an empty pan. (28-29)

In Vitro Release Study and Kinetic Analysis: The release characteristics of celecoxib from optimised C-SNEDDs and its suspension formulation, which contained 10 mg of celecoxib each, were compared using an in vitro drug release procedure. The dialysis method was used to perform the in vitro dissolution tests on C-SNEDDs. (30) A dialysis membrane (MWt of 12,000 kDa) was tied at one end of a glass cylinder that was open at both ends and fastened to the shaft of a United States Pharmacopoeia (USP) dissolving apparatus (31, 32). A beaker filled with 50 mL of isotonic phosphate buffer (pH 7.4) (dissolution medium) was used for in vitro drug release studies. The dissolving media was maintained at 37 ± 0.5 °C throughout these tests, which were carried out at 100 rpm. The same volume of celecoxib-free fresh isotonic phosphate buffer (pH 7.4) was introduced in place of three millilitres of sample from each formulation at regular intervals. (33) The amount of celecoxib in each sample was determined using spectrophotometry at 254 nm. (34) The calibration curve was used to plot the association between celecoxib concentration and spectrophotometric absorbance. Using the calibration curve, the concentration of celecoxib in the medium was computed at different time points. Three distinct models—Zero Order, First Order, and Diffusion—were used to collect the release kinetics data for the commercial formulation of celecoxib. (35, 36) These models offer useful information for the formulation and design of pharmaceutical products based on celecoxib, as well as insights into the behaviour of drug release.

Thermodynamic Stability Studies: In addition to being stored at the designated temperature for 48 hours, the stability of the optimised formulation was assessed under various stress conditions, including heating-cooling cycles (4 °C and 40 °C) and freeze-thaw cycles (-21 °C and +25 °C). (37) One millilitre of the formulation was diluted with one hundred millilitres of distilled water, centrifuged at 10,000 rpm for twenty minutes, and visually inspected for any phase separation in order to perform the centrifugation stress study.

3. RESULTS AND DISCUSSION

Screening of Components: The solubility and nano-emulsification performance of several oils with different saturation levels—more especially, medium- or long-chain triglycerides—was assessed. The oil that proved most effective in solubilising celecoxib was chosen because it had a big impact on the drug's solubility and absorption. Furthermore, a thorough screening process was used to determine the hydrophilic, non-ionic characteristics of the surfactants selected for this study—Cremophor El, Tween 20, Tween 80, Span 20, and Span 80—which are beneficial for emulsification and stability. An isothermal technique was used to assess celecoxib's solubility in a range of oils, surfactants, and co-surfactants (Figure 2). Of all the oils, sesame oil had the greatest concentration of solubilisation (30.65 mg/mL). It received an acceptable rating, suggesting that it could be a great carrier oil for applications involving the delivery of drugs. Due to their somewhat high concentrations, Labrafil, Capryol 90, and Labrafac were appropriate substitutes for sesame oil in a variety of formulations. The lower quantities of corn, soybean, almond, olive, and anise oils suggest that they can be included in compositions when a low oil concentration is desired.

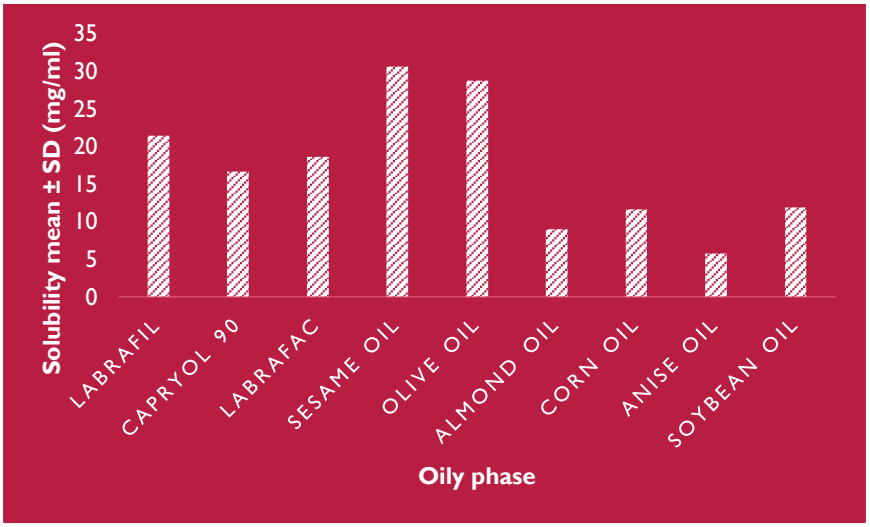

Figure 2: Solubility of celecoxib in various oils

Figure 3: Solubility of celecoxib in various surfactant & co-surfactant

According to the data, Tween 20 had the lowest concentration (46.86 mg/mL), while Span 80 had the highest concentration (67.86 mg/mL), followed by Tween 80 (49.67 mg/mL), Span 20 (55.64 mg/mL), and Cremophor RH 40. The particular medicine and the needs of the formulation determine which surfactant is best. Co-surfactants are added to formulations to improve drug absorption and solubility. PEG 400 had the highest concentration (67.75 mg/mL), according to the results, followed by propylene glycol (62.75 mg/mL) and trancutol (59.75 mg/mL). The particular formulation needs and compatibility with the surfactant determine which co-surfactant is best. In light of these findings, a ternary phase diagram was further constructed using sesame oil, span 80, and PEG 400 as the oil, surfactant, and cosurfactant, respectively.

Construction of Pseudo-Ternary Phase Diagram: A helpful tool for determining the ideal oil, surfactant, and cosurfactant composition for creating stable and effective C-SNEDDs was a pseudo-ternary phase diagram. The pseudo-phase diagram was created using sesame oil as the oil, span 80 as the surfactant, and PEG 400 as the cosurfactant, based on the findings of the solubility investigation. To ascertain the range of component concentrations necessary to create a stable nano-emulsion, ternary phase diagrams were created. The self-emulsification area was shown by the darker area in the phase diagram. Because of their greater hydrophilicity, it was shown that the addition of surfactant–cosurfactant increased the emulsification efficiency. With an oil concentration of up to 30% w/w, a stable system was observed. The system's ability to self-emulsify was shown to be enhanced by the addition of PEG 400, a cosurfactant. Furthermore, with less than 40% w/w of the surfactant in the system, it was found that spontaneous emulsion formation was inefficient. The findings also demonstrated that the oil content, surfactant, and co-surfactant all had an impact on the drug's solubility. The solubility of the medication diminishes as the oil concentration rises. On the other hand, medication solubility rises with surfactant and co-surfactant concentrations. This is because the medicine is dissolved in the nanoemulsion with the aid of the surfactant and co-surfactant. The study's findings served as a foundation for improving the C-SNEDDs' formulation.

Optimization of Formulation: An effective method for creating an ideal formulation with desired properties is the optimisation of C-SNEDDs. In accordance with a planned experimental strategy, the formulation variables—such as the concentrations of oil, surfactant, and co-surfactant—were changed. The statistical method used in the experimental design reduced the number of experiments needed while offering a thorough grasp of how each variable affected the response of interest. The ranges of concentrations for the essential ingredients of the C-SNEDDs formulation—oil, surfactant, and co-surfactant—were determined with the aid of the pre-optimization experiments. Oil, celecoxib, and co-surfactant concentrations were selected as independent variables and globule size, solubility, and transmittance percentage as responses in order to optimise the C-SNEDDs formulation. Globule size has a significant role in determining the C-SNEDDs' physical stability, and solubility has a significant impact on the drug's bioavailability. The formulation's transparency and clarity are gauged by the percent transmittance. Design Expert was used to create a total of 15 formulations based on the pre-optimization research. Table 1 displays the design matrix for the 15 formulations. The goal of this design was to determine the best formulation to get the intended results. The Design Expert software was used to analyse the design matrix, and a second-order polynomial equation was fitted to the responses. ANOVA was used to assess the model, and important components were found.

Table 1. The dependent and independent variables for the prepared SNEDDS using a mixture of experimental designs

Code	Oil (%) (X_1)	Surfactant (%) (X_2)	Co-Surfactant (%) (X_3)	Solubility (mg/mL) (Y_1)	Transmittance % (Y_2)	Size nm (Y_3)
F1	10	20	70	167.6	97	234.5
F2	10	30	60	254.1	95	342.6
F3	10	40	50	178.7	93	256.6
F4	20	40	40	156.6	99	110.6
F5	30	40	30	145.3	100	156.4
F6	10	50	40	159.7	95	198.7
F7	20	50	30	139.2	98	101.6
F8	30	50	20	123.6	94	179.4
F9	30	30	40	133.5	93	198.4
F10	10	60	30	189.6	97	106.5

F11	20	60	20	163.4	100	113.7
F12	30	60	10	107.3	99	116.2
F13	10	70	20	133.6	100	100.5
F14	20	70	10	115.3	89	110.6
F15	10	80	10	119.5	99	99.6

Better transparency of the C-SNEDDs was indicated by the design matrix results (Table 1), which demonstrated that the transmittance % (Y1) increased in tandem with the surfactant percentage (X1). Transmittance and particle size (Y3) were traded off, though, as the size shrank as the surfactant proportion rose. The solubility (Y2) and size (Y3) of the C-SNEDDs were also impacted by the co-surfactant percentage (X3) and oil percentage (X2). The results demonstrated that the samples exhibited good clarity, with transmittance values ranging from 92 to 100%. As indicated by the solubility values, which ranged from 107.3 to 254.1 mg/mL, the SNEDDS successfully increased the drug's solubility. The samples were in the nano-emulsion range, as shown by the C-SNEDDs' size range of 99.6 to 342.6 nm. A low to moderate degree of polydispersity was indicated by the PDI values, which varied from 0.117 to 0.312. On the other hand, the system's compositions, as indicated by the amounts of PEG 400 (X3), span 80 (X2), and sesame oil (X1), were the independent variables. The equations can be expressed in the generic form Y = aX1 + bX2 + cX3, where the coefficients a, b, and c stand for the contributions of each independent variable to the dependent variable. These coefficients' particular values were specific to the system and dependent variable under study and were derived by statistical analysis of experimental data, such as regression analysis.

The emulsification time varied between 41 and 89 seconds, suggesting that C-SNEDD preparation was not too difficult. The samples possessed a negative charge on their surface, as indicated by the zeta potential values, which varied from -26.4 to -13.8 mV.

Table 2. The dependent and independent variables for the prepared SNEDDS using a mixture of experimental designs

Code	% Drug content	Emulsification time (s)	PDI	Zeta potential
F1	76	67	0.265	−26.4
F2	68	89	0.303	−22.6
F3	88	56	0.256	−16.3
F4	79	64	0.201	−17.5
F5	84	79	0.153	−18.3
F6	59	50	0.187	−18.1
F7	75	55	0.312	−13.8
F8	77	69	0.273	−14.1
F9	84	77	0.117	−16.8
F10	74	63	0.198	−15.4
F11	89	49	0.204	−17.2
F12	90	63	0.198	−22.6
F13	75	41	0.297	−15.3
F14	72	48	0.243	−19.5
F15	78	45	0.179	−23.17

In order to find experimental settings where all desirability criteria were as closely met as possible, Design-Expert® was

used to choose the best factor settings based on the regression models. The goal of the design optimisation procedure was to maximise the transmittance and solubility while minimising the size of the globules. The software built and analysed an optimal formulation (F13) based on the provided optimisation parameters. Table 3 describes the composition of this optimised recipe. Celecoxib solubility was 133.6 ± 3.3, transmittance was 100%, and the optimised formula had a droplet size of 100.5 nm with a tiny PDI of 0.297. When the projected and experimental values of the optimum C-SNEDDs (F 13) were compared, they closely matched, with a tiny relative prediction error (less than 9%), indicating that the regression equations that were produced were valid.

Table 3. Composition of the optimized formulation system

Oil	Surfactant	Co-Surfactant
Sesame oil	Span 80	PEG 400
10	70	20

Differential Scanning Calorimetry Studies: A differential scanning calorimeter was used to produce thermograms of celecoxib, sesame oil, span 80, PEG 400, and the optimised formulation physical mixture, as illustrated in Figure 4. Every curve in this graphic denotes a distinct substance. The melting point and other thermal characteristics of each material, which are crucial factors influencing the stability and bioavailability of medications, were visible in the figure. Celecoxib, span 80, and PEG 400 all showed prominent endothermic peaks at about 150 °C, 60 °C, and 50 °C, respectively, suggesting that they have high melting points. This suggests that it may be more challenging for them to dissolve in water and be absorbed by the body. The optimised formulation F13 with sesame oil, on the other hand, had large endothermic peaks at about 40 to 50 °C, indicating lower melting temperatures. Because they are easily dissolved in water and absorbed by the body, these materials are better suited for drug delivery systems. The inhibition of celecoxib's crystallisation and solubilisation in the C-SNEDDs may be the cause of the alteration in the drug's melting behaviour. Thus, it might be said that celecoxib was amorphous in the C-SNEDDs.

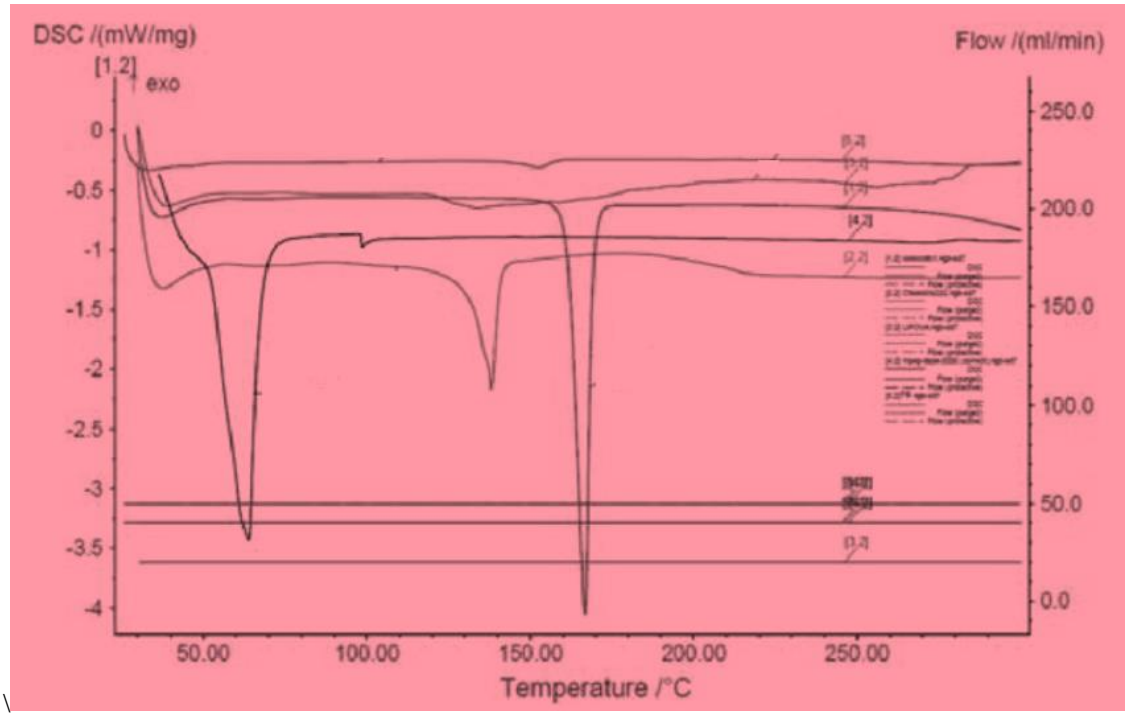

Figure 4: DSC of optimized formulation

In Vitro Release: The celecoxib suspension and the C-SNEDDs optimised formulation's in vitro release characteristics were contrasted. Celecoxib was seen to be released from the C-SNEDDs quickly at first. Figure 5 illustrates that the optimized-formula C-SNEDDs released over 92% of celecoxib at the same time, while the celecoxib suspension released less than 20% within 24 hours. The formulation C-SNEDDs had the lowest droplet size (100.5 nm), lowest PDI value (0.297), and greatest

PEG 400 concentration (20%), which allowed for the maximum release of celecoxib. Because the quantitative drug release from created nano-emulsions is reliant on droplet size, the formula yields a higher drug release rate. This promoted quick drug release by increasing the nano-emulsion's interfacial area with tiny drops. On the other hand, solid celecoxib particles suspended in a liquid medium made up a celecoxib suspension. As shown by the R-squared (R2) values, the kinetics study of the release data started by evaluating each model's goodness of fit (Table 4). The degree to which each model fits the experimental data is shown by the R2 value. The diffusion model was found to have the greatest R2 value (0.93453), indicating a very good fit to the celecoxib release kinetics. This finding implies that the drug's release behaviour from the suspension is best described by the diffusion model. A significant negative slope (−2.5674) was seen in the suspension's diffusion model, suggesting a high celecoxib release rate. This implies a rapid release of celecoxib from the suspension. On the other hand, the negative slope (-0.00764) in the First Order model for the nano-emulsion indicates a slow decline in celeccoxib concentration over time.

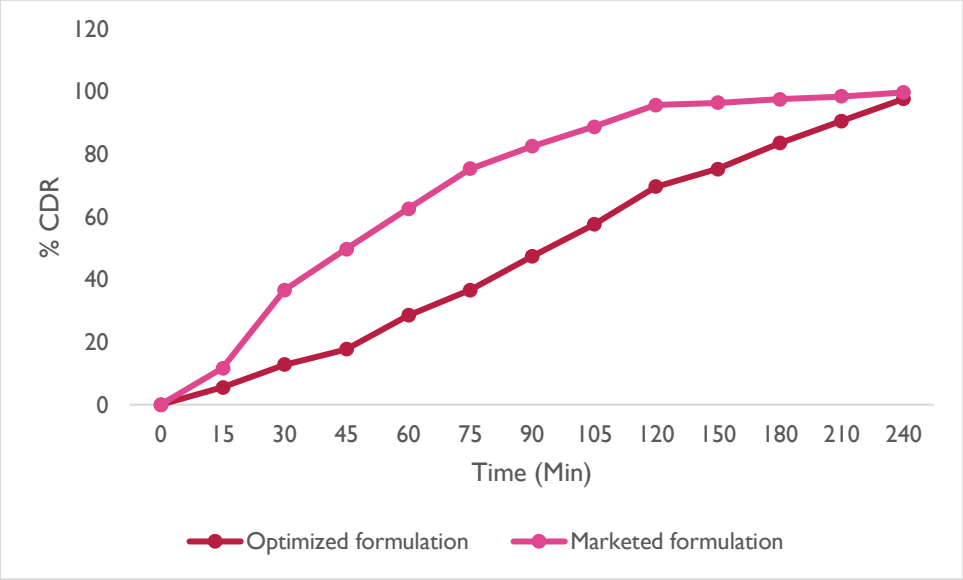

Figure 5: In vitro release of celecoxib from the optimized C-SNEDDs compared with the marketed formulation.

Table 4. Kinetics analysis of the release data

	Model		
	Zero	**First**	**Diffusion**
Slope	−0.03211	−0.00764	−2.5674
Intercept	95.6732	1.974323	99.7425
R^2	0.75986	0.787533	0.93453

The rate at which the celecoxib particles dissolved in the liquid medium determined how quickly the drug was released from the suspension. Celecoxib may dissolve slowly from the suspension due to its weak solubility, which would result in a slower release rate than that of the C-SNEDDs. In conclusion, it is clear that the nano-emulsion formulation has a number of benefits when contrasting the release kinetics of celecoxib in the solution with the self-nanoemulsifying drug delivery system. In parameter estimation, the nano-emulsion showed reduced variability, statistical significance, and a satisfactory match. In contrast to the quick release from the suspension, the nano-emulsion's slow-release profile indicates improved solubility and regulated release behaviour. These results highlight how well the nanoemulsifying system works to increase celecoxib's solubility and release kinetics, making it a viable strategy for the creation of pharmaceutical products.

Thermodynamic Stability: The batches were stable because there was no phase separation or precipitation seen upon centrifugation. The batches' stability was evaluated under a range of stress conditions, including RT at a predetermined temperature for 48 hours, heating-cooling cycles (4 °C and 40 °C), and freeze-thaw cycles (-21 °C and +25 °C). All of the batches were found to be stable under all of these conditions.

4. CONCLUSION

Celecoxib's SNEDDS were successfully created in this work, and their in vitro performance was evaluated. Because of their enormous surface area, these formulations' nanosized is what makes it easier to improve medication absorption and dissolution. Drug distribution to the lymphatic system is made possible by the lipidic composition of these systems. The technique used in the study to screen for SNEDDS excipients made it easier to comprehend how well different surfactants emulsify a particular oily phase. Additionally, it aided in the quick screening of the wide range of co-surfactants that were accessible for peroral administration. Additionally, the shorter emulsification period and smaller particle size may facilitate medication absorption. Based on these findings, SNEDDS may offer an effective dose form for a medication that is water insoluble when taken orally. It can be concluded that SNEDDS formed from sesame oil, span 80 and PEG is a promising approach to improve the solubility, dissolution rate and bioavailability of celecoxib because of the simple manufacturing process, low production costs and the possibility of manufacturing at industrial scale. The present study may serve as a prototype approach for the formulation development of other hydrophobic drugs as self-nanoemulsifying drug delivery system.

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