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Formulation, Optimization and Evaluation of Poorly Soluble Drug Snedds

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ABSTRACT

The goal of the study is to increase the oral bioavailability of kaempferol by creating a self-nanoemulsifying drug delivery system (SNEDDS). In the current work, a variety of oils, surfactants, and co-surfactants were used to manufacture kaempferol into SNEDDS. Numerous investigations, including droplet size and thermodynamic stability, drug content analysis, and in vitro drug release experiments, were conducted on the proposed formulations. The combination of Lauroglycol 90 as the oil phase, Poloxamer 188 as the surfactant, and Transcutol HP as the co-surfactant was chosen for the creation of SNEDDS of kaempferol after oils, surfactants, and cosurfactants were screened. The pseudo ternary phase diagram was used to optimise the formulation's composition. After evaluation, it was discovered that the optimised formulation had better in vitro drug release and good physical stability. When formulated as a self-nano emulsifying drug delivery system, a stable SNEDDS of kaempferol was created, and the results showed a significant improvement in the drug's dissolution, suggesting that it may improve the medication's oral solubility and bioavailability.

Keywords: *Self nanoemulsifying drug delivery system, kaempferol, In vitro evaluation, Oral bioavailability*

1. INTRODUCTION

Plant secondary metabolites known as flavonoids or plant polyphenols are distinguished by their diphenyl propane structure. They are common ingredients in fruits and vegetables and are found throughout the plant kingdom [1–3]. For thousands of years, India and other Asian nations have utilised several of them as traditional medicines. Because of their potent antioxidant capabilities, these plant polyphenols play a significant role in the nutritional and medicinal qualities of foods produced from plants. Because of their many pharmacological characteristics, antioxidant chemicals have drawn a lot of interest from researchers and consumers of natural goods. [4]

A common natural flavonoid that belongs to the subcategory of flavonols and is found in many plant-derived foods and plants used in traditional medicine, kaempferol is a yellow compound with a low molecular weight and molecular formula. It has been shown to have a number of therapeutic effects, including hepatoprotective, antioxidant, anti-inflammatory, and

anticancer properties. [5

9] However, due to its restricted membrane permeability and low lipid solubility, kaempferol has a relatively low oral bioavailability. Pteridophyta, Pinophyta, and Magnoliophyta are among the many botanical families where kaempferol has been detected. Kaempferol's absorption was found to be low to moderate, resulting in a poor bioavailability of about 2%. It freely dissolves in methanol and has a hydrophobic character [10].

An isotropic mixture of an oil, surfactant, co-surfactant, and drug, self-emulsifying drug delivery system (SEDDS) formulations can form an emulsion with water when gently agitated, just like in the gastrointestinal tract. [11] The medication is presented in the solubilised form by this spontaneous emulsion formation in vivo, and the wide interfacial area created by the droplets' small particle size encourages a faster rate and extent of absorption [12, 13]. A much more stable version of SEDDS, the Self-Nano Emulsifying Drug Delivery System (SNEDDS) has drawn special interest as a way to improve the oral bioavailability of drugs that are poorly absorbed [14, 15]. In order to overcome its low bioavailability, kaempferol was combined into the Self-Nano Emulsifying Drug Delivery System (SNEDDS) and tested in vitro.

MATERIALS AND METHODS

Materials: The supplier of kaempferol was TCI Chemicals (India), Pvt. Ltd. We bought Transcutol HP, Labrafac WL, Labrasol, Capmul MCM, and Labrafil from Gattefosse (Mumbai, India). We bought the various oils from SD-Fine Chemicals (Mumbai, India): rice bran oil, almond oil, sunflower oil, eucalyptus oil, and olive oil. Both Lauroglycol 90 and Cremophor RH 40 were supplied by BASF India Ltd. (Bandra East, Mumbai, India). Additional chemicals, such as HCl, PEG200, and polyethylene glycol-400 (PEG-400), were purchased from Acros Organics (Mumbai, India). Sigma Aldrich (St-Louis, MO, USA) provided the poloxin and other compounds. Every additional chemical and solvent employed in the investigation was of analytical quality.

Preliminary Screening: The oil, surfactant, and cosurfactant were chosen using the equilibrium solubility approach [16, 17]. The oil, surfactant, and co-surfactant were chosen based on how soluble kaempferol was in each component. A range of oils, surfactants, and co-surfactants were used for the screening. 1.5 mL of each oil, surfactant, and co-surfactant were placed to a clean glass vial, along with an excess of kaempferol. After correctly capping the vials, they were shaken for 72 hours at 37 ± 0.5 °C on a mechanical shaker. After five minutes of centrifuging the samples at 10,000 rpm, the supernatant was extracted. Following an appropriate dilution, the amount of kaempferol dissolved in each component was measured at 266 nm using a UV spectrophotometer (UV1800, Shimadzu, Japan).

Pseudo ternary phase diagram: Each of the three components—oil (Lauroglycol 90), surfactant, co-surfactant (Smix, also known as Poloxamer188: Transcutol), and water content—represents an apex of a triangle in a phase diagram. After precisely weighing the necessary quantities of the ingredients (oil and Smix), they were sonicated for three minutes. To create a uniform mixture, the fluid was then vortexed and gradually heated to 45 to 50 °C. Drop by drop, distilled water was added to this mixture until a clear solution was achieved. The mass ratios of the surfactant and co-surfactant (Smix) were changed to 1:1, 1:2, 2:1, and 3:1. [18] These ratios were used to create pseudo-ternary mixtures, and the amount of water that created a transparent solution was then shown with other elements in the pseudo-ternary phase diagram [19].

Preparation of liquid SNEDDS: Several formulations were carefully selected from each generated phase diagram's zone of nanoemulsions with the goal of having an oil phase concentration that could dissolve 0.05% w/v of kaempferol. Kaempferol was dissolved in oil at two different concentrations: 0.015% w/v and 0.05% w/v. The surfactant and co-surfactant mixture was then mixed in the oil phase in the proper amount, and deionised water was added dropwise while being constantly vortexed until a clear, transparent monophasic liquid state formed. [20, 21]

Evaluation of SNEDDS formulation

Percentage drug content: The drug content of the chosen formulations was assessed. The formulation was then diluted with methanol, and a UV spectrophotometer was used to detect absorbance at 266 nm. [22]

pH of SNEDDS: Five millilitres of distilled water were used to dissolve 100 µl of SNEDDS. At room temperature, the pH of the nanoemulsion was determined using a pH meter. Prior to and during dilution with the aqueous phase, the pH of SNEDDS was determined [23].

Self-Emulsification time and robustness to dilution: 100 ml of 0.1N HCl, 100 ml of Phosphate Buffer pH 6.8, and 100 ml of distilled water were combined with kaempferol (0.015% w/v and 0.05% w/v) at 37 °C with mild stirring using a magnetic stirrer in order to calculate the emulsification time (the amount of time required to reach the emulsified and homogeneous mixture, upon dilution). Visual evaluation of the formulation was conducted based on the emulsion's final appearance and emulsification rate [24, 25].

Thermodynamic stability studies: To determine any phase separation and the stability of the resulting nanoemulsion, thermodynamic stability tests were performed on the formulation [26].

Centrifugation study: A centrifuge (CPR-30-PLUS, Remi Equipments, Mumbai, India) was used to centrifuge the formulation for 30 minutes at 18,000 rpm. Phase separation, creaming, cracking, and other instability issues were then examined in the final formulation. [27]

Heating and cooling cycle: In an incubator (Remi, Mumbai, India), the liquid SNEDDS formulations underwent a heating-cooling test with six refrigerator cycles at 45 °C and 4 °C temperatures independently for 48 hours. It was then evaluated for phase separation. [28]

Cloud point measurement: The diluted formulation was gradually heated on a water bath to establish its cloud point temperature, and the thermometer was used to record the temperature at which cloudiness appears. Distilled water was used to dilute the formulation in a 1:100 ratio. A water bath was used to progressively raise the temperature of the diluted samples. The temperature at which cloudiness appeared suddenly was identified as the cloud point [29].

Viscosity studies: Using a small sample adapter of the Brookfield viscometer (ViscoQC100, Anton Paar), the viscosity of the optimised formulation was determined in triplicate at 12 rpm and room temperature (25±1 °C) [30].

Particle size: Using a particle size analyser (Litesizer 500, Anton Paar), the chosen formulation's particle size was ascertained. The measurements were taken at a fixed angle of 90° and at 25 °C. Using a particle size analyser, aliquots of the formulation were serially diluted with filtered water to determine the particle size [31].

In vitro drug release: Using a USP paddle dissolution equipment, kaempferol from Opt-KF3, KF11, KF12, and KF15 was investigated. To replicate stomach conditions, the release media (0.1 N HCl, pH-1.2, 900 mL) was put in a basket and kept at 37±0.5 °C. The sample was knotted at both ends and put in a dialysis bag (MW CO-12 kDa). The dialysis bag revolved at 100 rpm after being fastened to a paddle and plunged into a dissolving media. Five millilitres of the sample, appropriately diluted and filtered, were taken out at a specified time. At 266 nm, the absorbance was measured using a UV visible spectrophotometer [10, 29]. A graph was produced between the percentage of drug release and time after the release was computed. For comparison, a similar investigation was conducted with pure kaempferol under comparable conditions. To assess the release kinetics and release mechanism, the release data was fitted to a variety of kinetic models. [32]

RESULTS AND DISCUSSION

Preliminary Screening: Kaempferol's solubility in various oils, surfactants, and co-surfactants is depicted in Figure 1A–C. The selection process was based on which oil had the maximum solubility. The sequence of kaempferol solubility in various oils is as follows: Lauroglycol l90 > Caprol PGE-860 > Olive oil > Eucalyptus oil > Rice bran oil > Almond oil > Sunflower oil (Fig. 1A). Transcutol HP > PEG400 > PEG200 > PG> Isopropyl alcohol > Poloxamer188 > Solutol HS 15> Cremophor RH 40 > Tween 20 > Span 20> Tween 80> Span 80 and The order of kaempferol solubility in surfactant and co-surfactant is Koliphor HS15 (Fig. 1B-C). Transcutol HP (48.74 ± 2.55 mg/mL), Lauroglycol 90 (37.97± 2.11 mg/mL), and Poloxamer 188 (84.23 ± 3.43 mg/mL) were used as oil, surfactant, and co-surfactant, respectively. When SNEDDS come into contact with water, it enables them to emulsify rapidly.

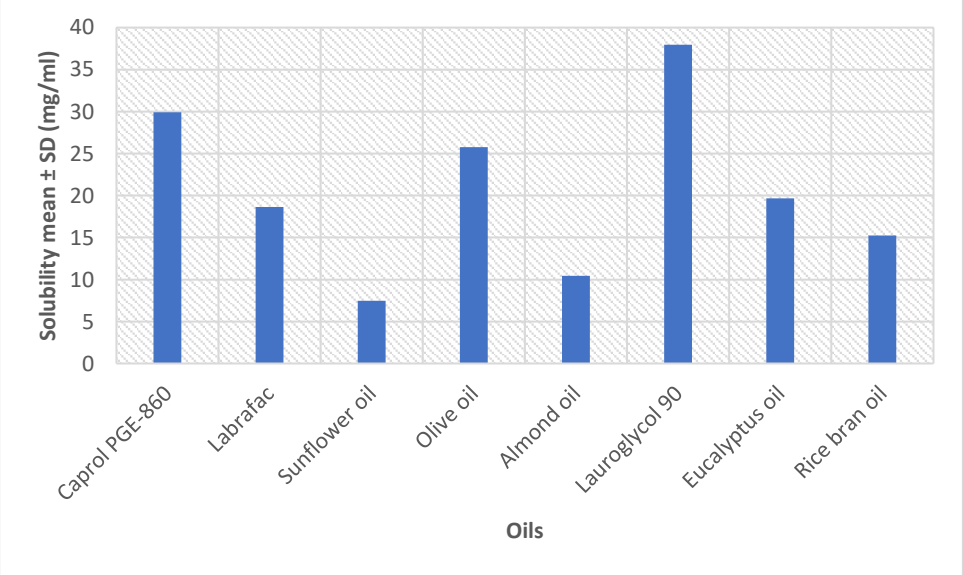

Figure 1A: Solubility of kaempferol in various oils. Study performed in triplicate and results shown as mean ± SD.

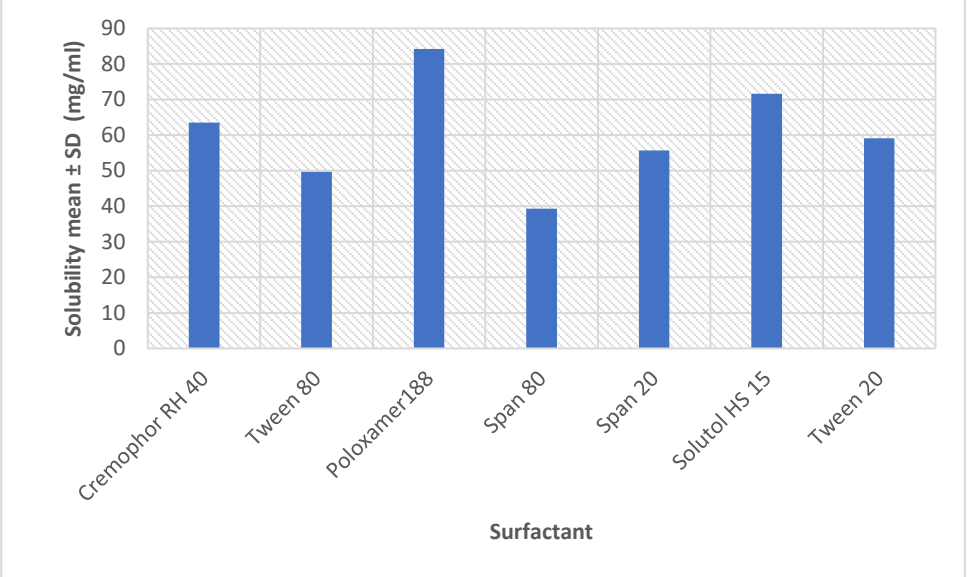

Figure 1B: Solubility of kaempferol in various surfactant. Study performed in triplicate and results shown as mean ± SD.

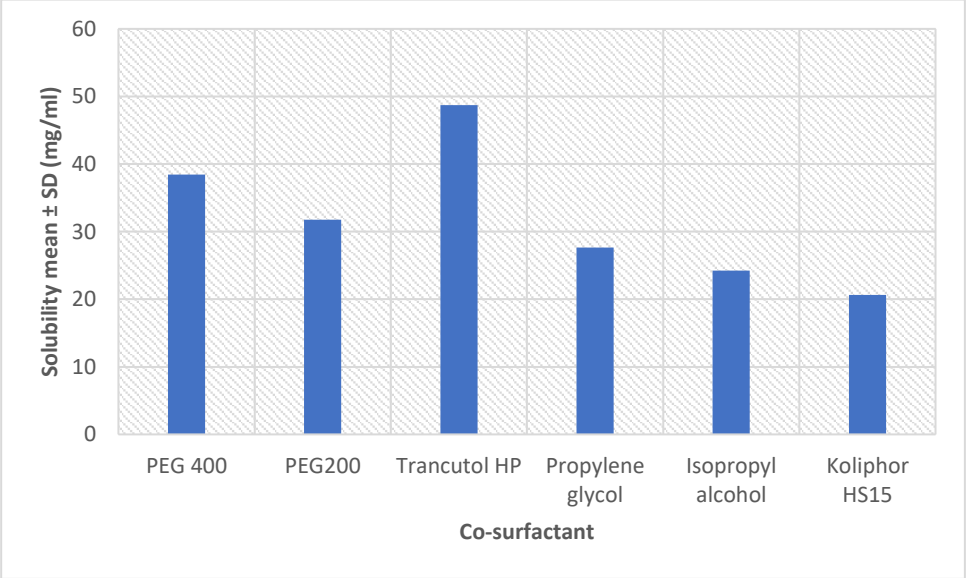

Figure 1C: Solubility of kaempferol in various Co-surfactant. Study performed in triplicate and results shown as mean ± SD.

Solubility of kaempferol in screened mixture: In order to create formulations KF1 through KF16, the mixture was further put through an emulsification study with the inclusion of various co-surfactants (Lauroglycol 90, Poloxamer 188, and Transcutol HP) with each of the chosen mixtures in the oil:surfactant:co-surfactant ratio, i.e. 1:1, 1:2, 2:1, and 3:1. When transcutol was employed as a co-surfactant with Lauroglycol 90 (oil) and Poloxamer (surfactant), it was discovered that the transmittance should be at its highest in the case of KF11. Moreover, there was no noticeable turbidity or phase separation.

Pseudo ternary phase diagram: As seen in Figure 2, a variety of oil ratios (9:1, 1:9) and surfactant and co-surfactant ratios (1:1, 1:2, 2:1, and 3:1) were investigated in order to produce a clear and stable SNEDDS. When compared to the other surfactant and co-surfactant ratios of 1:1, 1:2, and 3:1, the optimal ratio (Smix) was found to be 2:1, which showed a clear zone.

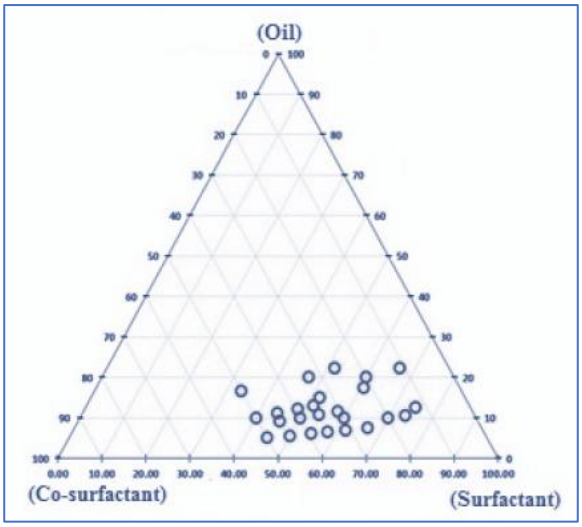

Figure 2. Pseudo ternary phase diagram of different Smix ratios: 2:1.

According to the phase diagram, oil (Lauroglycol 90, 9–27%, w/w), surfactant (Poloxamer 188, 29–75%, w/w), and co-surfactant (Transcutol HP, 9–57%, w/w) were used for the optimisation and preparation of SNEDDS. This is because the absorption of surfactant at the oil-water interface, which lowers interfacial tension, may account for the transparency of the zone in the Smix 2:1 ratio.

Preparation of SNEDDS: Table 1 shows the many formulations of SNEDDS that were created by adjusting the concentrations of oil, surfactant, and cosurfactant based on the pseudoternary phase diagram results.

Table 1: Different formulations of SNEDDS varying percentage compositions of components

Code	Nanoemulsions composition (%, w/w)			Smix ratio
	Oil	Surfactant	Co-surfactant	
KF1	19.64	40.32	40.32	1:1
KF2	29.98	35.95	35.95	1:1
KF3	32.64	34.43	34.43	1:1
KF4	39.56	30.23	30.23	1:1
KF5	19.64	27.53	54.23	1:2
KF6	35.65	22.43	42.16	1:2
KF7	28.44	24.43	47.98	1:2
KF8	39.11	20.43	39.53	1:2
KF9	19.56	52.53	28.54	2:1
KF10	29.56	45.53	25.51	2:1
KF11	29.65	38.64	21.64	2:1
KF12	49.75	31.64	18.72	2:1
KF13	19.21	58.43	21.92	3:1
KF14	29.53	51.24	19.32	3:1
KF15	38.56	43.87	17.28	3:1

KF16	49.52	36.39	14.64	3:1

Evaluation of SNEDDS formulation

Percentage drug content of SNEDDS: A % drug content study was performed on the produced formulation. The majority of the formulations had a high drug content, with 95.97±3.54 to 100.01±2.98 percent of Kaemferol put into the formulation, according to Figure 3.

pH of liquid SNEDDS containing kaempferol: A pH analysis of a few SNEDDS that contained Kaemferol revealed that all of the formulations' pH values fell between 5.98±0.019 and 7.11±0.021.

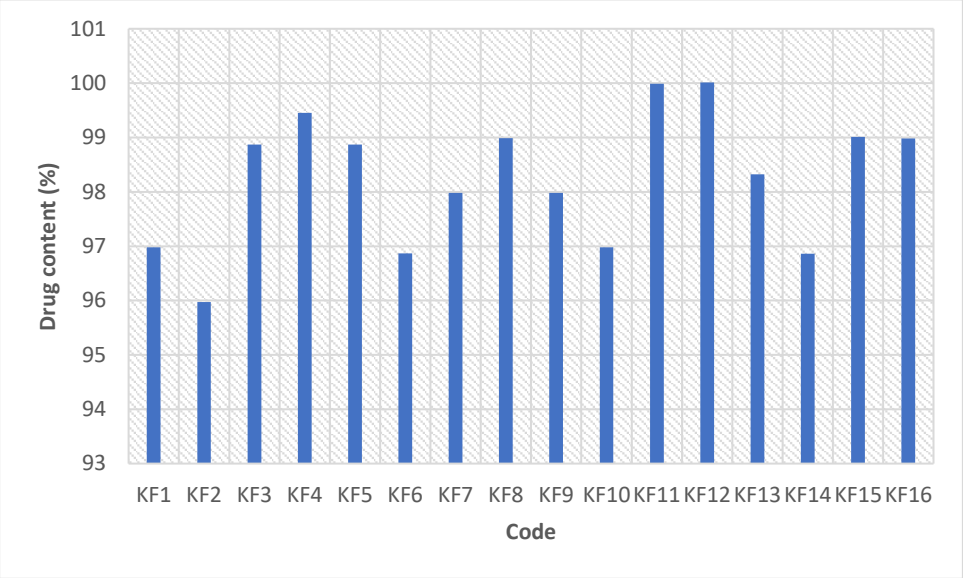

Figure 3: Percentage drug content of SNEDDS formulations (KF1-KF16)

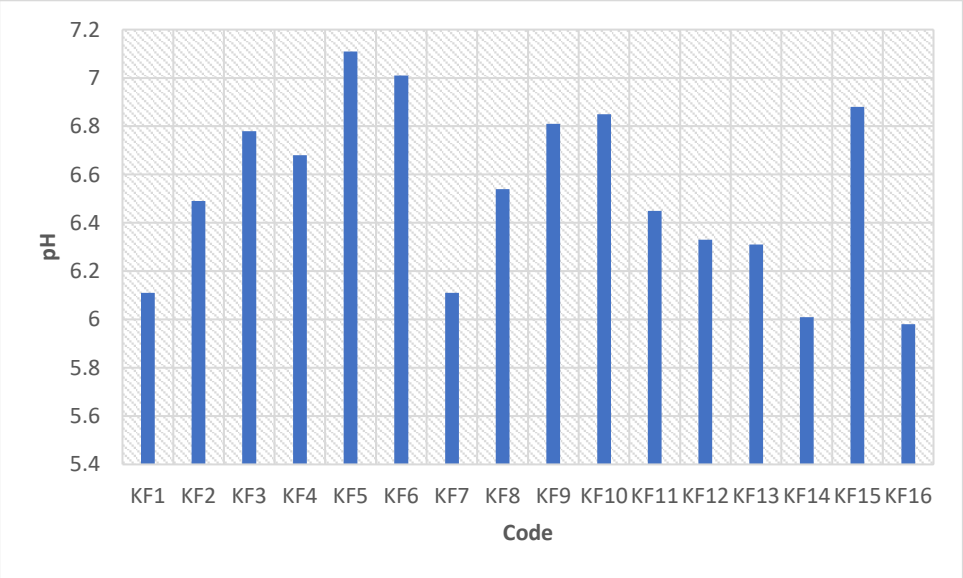

Figure 4: pH of SNEDDS formulations (KF1-KF16)

Self-emulsification time and robustness to dilution: The medication used to prepare the nanoemulsion was initially 0.05% w/v of the emulsion, and precipitation was seen in all of these formulations using 0.1N HCl and a pH 6.8 solution of phosphate buffer. But when the supplied kaempferol is reduced to 0.015% w/v, all of the formulation forms a nanoemulsion in 8 seconds when it is diluted into a solution of 0.1N HCl and Phosphate Buffer pH 6.8. However, even after 24 hours, it

was discovered that the formulations KF3, KF11, KF12, and KF15 had a distinct translucent look in terms of stable homogeneity and transparency. Regarding distilled water, it was discovered that every formulation had a transparent, yellowish look.

Thermodynamic stability studies:

Centrifugation study: After centrifugation, it was discovered that all three of the chosen SNEDDS formulations (KF3, KF4, KF5, KF8, KF9, KF10, KF11, KF12, and KF15) were stable. The formulations showed no evidence of phase separation. Phase separation, creaming, and cracking are not observed in the thermodynamically stable nanoemulsions that resulted from the optimised SNEDDS formulations. No phase separation, creaming, or cracking was seen in the optimised SNEDDS tested for centrifugation and the heating-cooling cycle.

Table 2: Centrifugation, Heating and cooling cycle study of SNEDDS

Code	Appearance	Heating (40 °C)	Cooling (4 °C)
KF1	Unstable, phase separation	Unstable, phase separation	Unstable, phase separation
KF2	Unstable, phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF3	Homogenous, no phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF4	Homogenous, no phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF5	Homogenous, no phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF6	Unstable, phase separation	Unstable, phase separation	Unstable, phase separation
KF7	Unstable, phase separation	Unstable, phase separation	Unstable, phase separation
KF8	Homogenous, no phase separation	Unstable, phase separation	Unstable, phase separation
KF9	Homogenous, no phase separation	Unstable, phase separation	Unstable, phase separation
KF10	Homogenous, no phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF11	Homogenous, no phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF12	Homogenous, no phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF13	Unstable, phase separation	Unstable, phase separation	Unstable, phase separation
KF14	Unstable, phase separation	Unstable, phase separation	Unstable, phase separation
KF15	Homogenous, no phase separation	Homogenous, no phase separation	Homogenous, no phase separation
KF16	Unstable, phase separation	Homogenous, no phase separation	Homogenous, no phase separation

Cloud point measurement: An essential component of the self-emulsifying formulation's stability is the estimation of cloud spots. The temperature at which self-emulsifying substances dehydrate and change from a clear to a cloudy dispersion may have an impact on drug absorption. This is known as the cloud point. Therefore, the self-emulsifying formulation's cloud point ought to be higher than body temperature (37 °C). The cloud points of KF3, KF11, KF12, and KF15 showed that stable SNEDDS would form at physiological temperature.

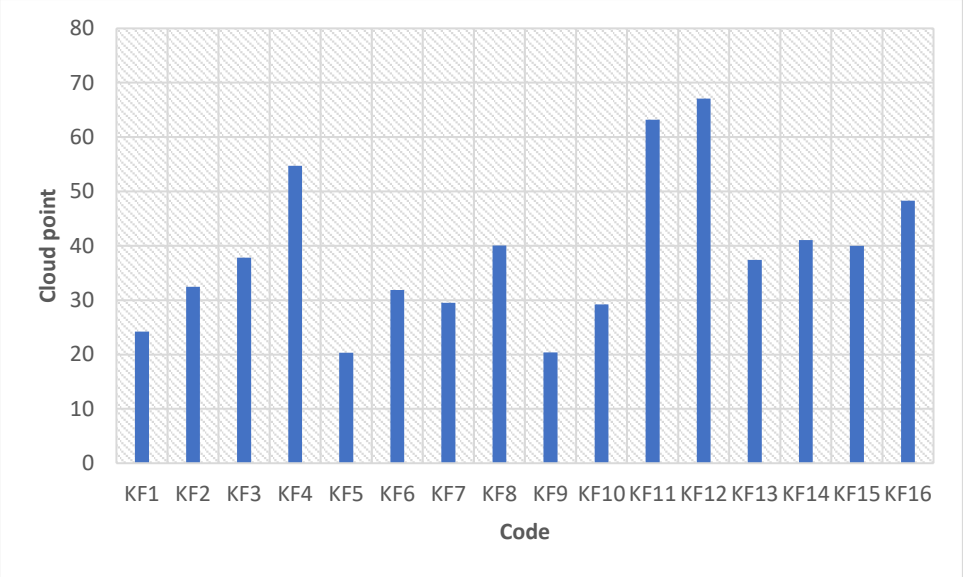

Figure 5: Cloud point measurement of liquid SNEDDS containing kaempferol

Viscosity studies: Based on the enlisted formulas, the viscosity was estimated to be between 183.54±3.56 and 255.33±3.22 cP. Additionally, the smaller droplet size of SNEDDS is primarily responsible for its reduced viscosity.

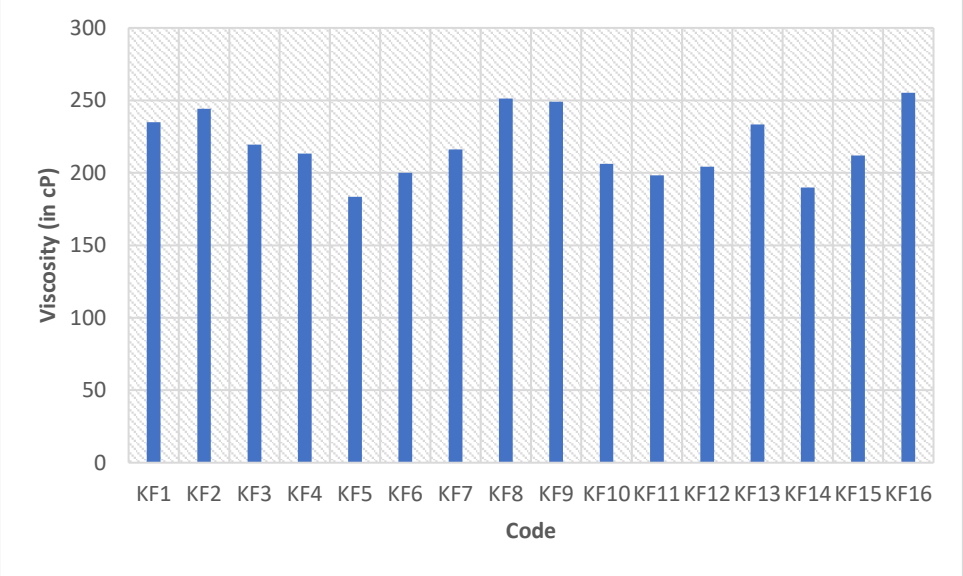

Figure 6: Viscosity of the liquid SNEDDS containing kaempferol

Determination of particle size: Table 3 revealed that the KF11 formulation had a lower PDI and particle size than the other two formulations. For KF11, the percentage polydispersity index was 26.22% and the particle size was measured at 56.86 nm.

Table 3: Particle size of the liquid SNEDDS containing kaempferol

Code	**Particle size**	% PDI
KF3	100.12	24.22
KF11	56.86	26.22
KF12	88.22	29.43

KF15	98.22	31.54

In-Vitro Drug Release: Figure 6 shows the results of the release investigation of pure kaempeferol dispersion and Opt-KF3, KF11, KF12, and KF15. Opt-KF3, KF11, KF12, and KF15 showed a quick release of 20.21%, 21.64%, 19.54%, and 16.43% in the first two hours, and a longer release of 82.43, 95.64%, 73.32%, and 69.44% in the next twenty-five hours. The first quick release may be explained by the presence of kaempferol on the surface of SNEDDS. Longer-lasting medication release was made possible by the substance that was confined inside SNEDDS. The drug release from the kaempferol dispersion was found to be extremely low throughout that time, at 48.54%. The poor solubility of kaempferol may be the cause. After submitting the Opt-KF11 formulation's release data to a number of kinetic models, the first-order model showed the best fit (R2 = 0.99543). The release exponent of n = 0.7264 showed that the release mechanism was of the non-Fickian transport type.

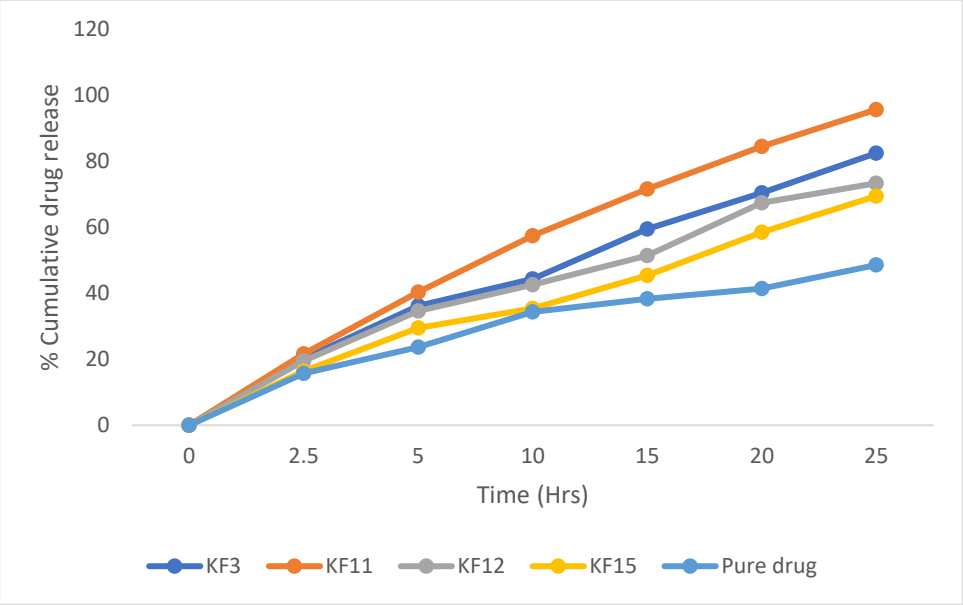

Figure 7: In-vitro drug release data

2. CONCLUSION

In this study, kaempferol was formulated into a stable dosage form with enhanced bioavailability using self-emulsifying technology. After screening a number of oils, surfactants, and cosurfactants, Lauroglycol 90, Poloxamer 188, and Transcutol HP were chosen for the creation of SNEDDS of kaempferol, respectively, based on solubility and transmittance investigations. The region of nanoemulsion production was identified using a pseudo ternary phase diagram, and SNEDDS with a drug content of 95–100% and an appropriate pH of 5.98±0.019 to 7.11±0.021 were then generated. Self-emulsification ability and robustness to dilution were used to optimise formulations, and stability and in-vitro dissolution were further assessed for the optimised formulation. The optimised formulation demonstrated low viscosity, better dissolving behaviour, acceptable particle size (≤150 nm), and strong thermodynamic stability. The maximal drug release of kaempferol (95.64%) was observed after 24 hours, which is an in vitro sign of increased bioavailability. The results obtained from the study confirmed the benefits of the medicinal plants. In fact, some flavonoids present in them demonstrated a low toxicity effect and stable SNEDDS of kaempferol with improved bioavailability is supported by the results.

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