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Original Article

PREPARATION AND *IN VITRO* EVALUATION OF SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEMS OF KETOPROFEN

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ABSTRACT

Objective: The aim of this study was to formulate, evaluate and characterise nanoemulsion formulation containing a lipophilic drug, Ketoprofen.

Methods: Nanoemulsion formulations composed of oil, surfactant, co-surfactants and Ketoprofen were prepared. In all formulations, the percent of surfactants, as well as oil, was varied while the amount of Ketoprofen kept constant. Solubility studies were conducted to select the oil, surfactant and cosurfactant. Phase diagrams were constructed using the aqueous phase titration method. Formulations were selected from the phase diagrams. The prepared nanoemulsions were subjected to different thermodynamic stability tests.

Results: Following optimization, the F7 formula (10% oil, 3:1 surfactant to co-surfactant) was thermodynamically stable, with a droplet size of 105 nm and a zeta potential of-26.21 mV. *In vitro* release study showed that the drug release pattern from formulations F5, F6, F7, F8, F9 and F10 was higher than that of F1, F2, F3 and F4.

Conclusion: The present work demonstrates that the nanoemulsion is a promising drug delivery system approach for the enhancement of solubility and dissolution rate of Ketoprofen.

Keywords: Nanoemulsion, Dissolution, Ketoprofen, Optimization

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INTRODUCTION

Oral delivery system of drugs considers the most popular and preferable route of drug administration where the medications could be easily administered via this route in comparison with other routes. Due to the appearance of some complications, these routes may be unwanted by patients and lead to patient compliance. These complications include injuries because of needle sticks, local reaction, cross-infection, high cost and dosage forms with a restricted number. Many of marketed drugs are formulated and admistered by the oral route. However, these drugs may lose some clinical effects due to some issues related to the physicochemical properties of drugs as well as physiological factors. The oral absorption of drugs may be limited by aqueous solubility and/or permeability [1, 2].

Many strategies have been employed in formulation approaches to improve the oral bioavailability of drugs through enhancing their solubility. These strategies involve salt formation, pH adjustment, micronization, and amorphization. However, there are some limitations, for example, salts upon formation, may return back to their original forms of base or acid and result in aggregation in the gastrointestinal tract (GIT) [3]. Reduction of particle size may be unwanted in conditions where poor wettability or handling difficulties are experienced for finer powders [3]. To avoid these drawbacks, many technologies have been invested in involving the use of nanoparticles, cyclodextrins, permeation enhancers and solid dispersions. Recently, efforts have focused on lipid-based drug delivery systems such as emulsions, liposomes, solid lipid nanoparticles and self-emulsifying drug delivery system [4].

Self-emulsifying drug delivery system (SEDDS) can be defined as isotropic mixtures of oils (natural or synthetic), surfactants (solid or liquid) and one or more co-surfactants (CoS). When there is a mild agitation accompanied by dilution with GIT fluids, SEDDS can produce fine droplets of oil in water (O/W) emulsion or microemulsions. Emulsions formed by SEDDS have droplet size ranging from 100 to 300 nm while transparent microemulsion produced by a self-micro emulsifying drug delivery system (SMEDDS), is characterised by a droplet with a size of less than 50 nm. In comparison to the emulsion, formulations of SEDDS are physically stable and their manufactured is easy. With respect to lipophilic drugs that show absorption limited by a dissolution rate, these systems can enhance and improve the extent and rate of absorption and produce plasma drug concertation-time curve with more reproducibility [5, 6].

Ketoprofen (KET), a non-steroidal anti-inflammatory drug (NSAID), is a safe and potent propionic acid derivative used widely in the treatment of osteoarthritis, ankylosing spondylitis, rheumatoid arthritis, and acute gouty arthritis. However, it possesses poor aqueous solubility, which may limit its oral bioavailability and consequently affects its therapeutic effect [7]. In this study, Ketoprofen was formulated as a self-emulsifying drug delivery system where the aqueous solubility can be enhanced and the oral bioavailability is improved.

MATERIALS AND METHODS

Materials

Ketoprofen was obtained from Hangzhou Hyper chemicals, China. Cumin oil, fenugreek oil, garlic oil and triacetin were purchased from hyper chem, China. Tween 80 and Tween 20 were supplied from CDH, India. Triton X (TX), Propylene glycol (PG) were obtained from Thomas Baker, India. Transcutol® HP was obtained from Gattefosse Corporation (USA). Oleic acid, ethanol and clove oil were supplied from G. C. C., UK

Methods

Determination of melting point

Differential scanning calorimetric analysis (DSC) was used to determine the melting point of pure drugs. Sample of 5 mg of pure drug was loaded into an aluminum pan sealed utilising a crimper and heated at a rate of 10 °C/min under the atmosphere conditions [8].

Powder X-ray diffraction (PXRD)

XRD was used to determine the crystallinity of pure drug using a MiniFlex II powder X-Ray diffractometer (Rigaku, United States). The radiation was delivered from a copper source operating at a voltage of 40 KV and a current of 40 mA. A continuous 2θ scan was

carried out in the range of 5-50° with a step width of 0.02° 2θ and a scanning speed of 2° min^{-1} [9].

Determination of the (λmax) of Ketoprofen

The maximum wavelength (λmax) of KET was measured using ethanol where 6 µg of KET in 1 ml of ethanol was diluted two times then the (λmax) of KET is recorded after scanning by UV-Visible spectrophotometer instrument.

Construction of calibration curve

Calibration curve of KET was performed by plotting the concentration of the drug prepared from stock solution against the absorbance. Standard solution of KET (100µg/ml) was prepared and a serial dilution was used to prepare different concentrations of stock solution of KET. The absorbance of KET solution was determined using UV-Vis spectroscopy (UV 1800 Shimadzu). The correlation coefficient (R^2) was employed in determining the linearity of the regression.

Solubility studies

The solubility of KET in different oils (clove oil, fenugreek oil, cumin oil, triacetin, garlic oil and oleic acid), surfactants (Tween 80, Tween 20 and TX) and co-surfactants (Propylene glycol, Transcutol® HP) was measured. KET was added in excess amount to 5 ml of each excipient in a cap vial. After sealing, these vials were kept in a water bath shaker for 72 h at 25±5 °C to provide a proper mixing of KET in the vehicles. When equilibrium is reached, centrifugation of cap vials was carried out at 300 rpm for 10 min. Undissolved KET was discarded by filtration using membrane filter (0.45 µm) and the supernatant was then taken and diluted with ethanol for analysis to quantify the content of soluble KET using UV-spectroscopy [10].

Construction of phase diagrams

Construction of a pseudo-ternary phase diagram is an important tool for screening of self-dispersible formulation components and to assess the effect of different components on *in vitro* performance of the formulation. It is useful to determine the best emulsification region of oil, surfactants and co-surfactants combinations by plotting each of them as an apex triangle. The components of the diagram are placed in a glass vial and vortexed at 25 ºC [11].

Formulation of a self-emulsifying drug delivery system

A number of SEDDS formulations were prepared where the components of each formulation were oil, surfactant, co-surfactants and KET. In all formulations, the ratios of surfactants as well oil was varied were varied while the amount of KET was constant. Mixture of oil, surfactant, co-surfactant and drug in a screw cap vial was mixed using vortex mixer and then heated for 30 min at 50 °C in a water bath to aid in homogenization and solubilization. Surfactant was mixed with Propylene glycol in the ratio of 1:1, 1:2, 1:3, 1:4, 2:1, 3:1 and 4:1 (w/w). Surfactant and the co-surfactant blend was mixed with oil in a ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 9:1 (w/w) [12] (table 1).

Evaluation of self-emulsification time

USP II dissolution test was employed in the evaluation of the emulsification time of SEDDS of KET. One ml of prepared formula was added to 500 ml of 0.1N HCl at 37 °C and the dissolution paddle was rotated at 50 rpm to provide a gentle mixing. Emulsification time was assessed visually where a homogenous phase was observed. One minute represents the optimum time required for the production of transparent SEDDS where a longer time may lead to a milky appearance [13, 14].

Dilution study

One ml of SEDDS formula of KET was diluted to 100 ml of distilled water, 0.1 N HCl and phosphate buffer (pH 6.8). The diluted preparation was left overnight and observed for any signs of phase separation [12].

Table 1: Composition of different SEDDS formulation containing Ketoprofen

Formulation code	Oil: S mix ratio	Clove oil %	Tween 80 %	Transcutol %	S: CoS ratio
F1	1:9	10%	45%	45%	1:1
F2	1:9	10%	30%	60%	1:2
F3	1:9	10%	22.50%	67.50%	1:3
F4	1:9	10%	18%	72%	1:4
F5	1:9	10%	60%	30%	2:1
F6	2:8	20%	53.40%	26.70%	2:1
F7	1:9	10%	67.50%	22.50%	3:1
F8	2:8	20%	60%	20%	3:1
F9	1:9	10%	72%	18%	4:1
F10	2:8	20%	64%	16%	4:1

Thermodynamic stability evaluations

The prepared formulations of KET-SEDDS were categorised into 3 sets, stored at room temperature, 40 °C and 4C ° for 48 h. Formulations that are stable at these temperatures were exposed to a centrifugation test at 3000 rpm for 30 min. After centrifugation, formulations that revealed no phase separation were evaluated using a freeze thaw test where each formula was exposed to three cycles of freeze thaw between-21 °C and 25 °C for 48 h [15].

Measurement of droplet size, polydispersity index and zeta potential

Droplet size and size distribution (polydispersity index) were measured using ABT-9000 nanolaser (Brookhaven, USA). All measurements were performed at 25 °C. Prior to measurements, SEDDS dispersions were diluted 10 times with purified water for size measurement. Zeta potential analyser (nano brook zeta plus, USA) was used for the determination of zeta potential of prepared formulations of KET-SEDDS [16].

Drug release study

In vitro release study of KET-SEDDS was carried out using USP dissolution apparatus II (Erweka DT720 GmbH, Germany). KET-SEDDS were filled in size '2' hard gelatin capsules were placed in the dialysis tubing. The release profile of KET-SEDDs was studied in dissolution vessels containing 900 ml of 0.1 N HCl. The dissolution apparatus was rotated at 50 rpm and maintained at 37 °C. At predetermined intervals, a 5-ml sample of release medium was withdrawn and replaced with an equal volume of fresh medium to maintain a constant volume. Samples were then measured using a UV-Visible spectrophotometer at 260 nm [10, 17].

RESULTS AND DISCUSSION

Measurement of melting point

Melting point of KET was determine to be 97.28 °C as shown in fig. 1. This indicates the crystallinity of powdered KET employed in this study [18].

X-ray diffraction study

The XRD diffractogram of ketoprofen was shown in fig. 2. Sharp distinct characteristic peaks at 2θ diffraction angles for Ketoprofen at 13°, 14.5°, 18° and 22.5° indicated its crystalline state [9].

Determination of maximum wavelength

UV-Vis spectroscopy was employed as an analysis technique for the determination of KET content in the solution. A λmax at 260 nm was

determined by a wavelength scan of a 6 µg/ml KET solution as shown in fig. 3 [19].

Construction of calibration curve

Calibration curve was constructed by plotting the absorbance against the diluted concentrations of the stock solution of KET. Absorbance readings over the range of concentrations were found to be linear, possessing a correlation coefficient (R^2) of high value (fig. 4).

Determination of KET saturated solubility

Selection of appropriate oil, surfactant and co-surfactant is crucial prior to their use in the formulation of a self-emulsifying drug delivery system. Drug solubility in components of SEDDS is essential because it invariably affects the drug loading efficiency and, subsequently the efficiency of SEDDS [20]. An important factor should be considered when formulating a SEDDS is to avoid precipitation of the drug upon dilution with gut fluid. Therefore, the components of SEDDS should possess high solubilization effect for the drug [21]. The saturated solubility of KET in various oils, surfactants and co-surfactants was measured. Various oils were screened for KET solubilisation, among which clove oil demonstrated the highest solubility (fig. 5). Amongst surfactants and co-surfactants, Tween 80 and Transcutol HP, respectively, revealed the highest solubility toward KET (fig. 6) and (fig. 7).

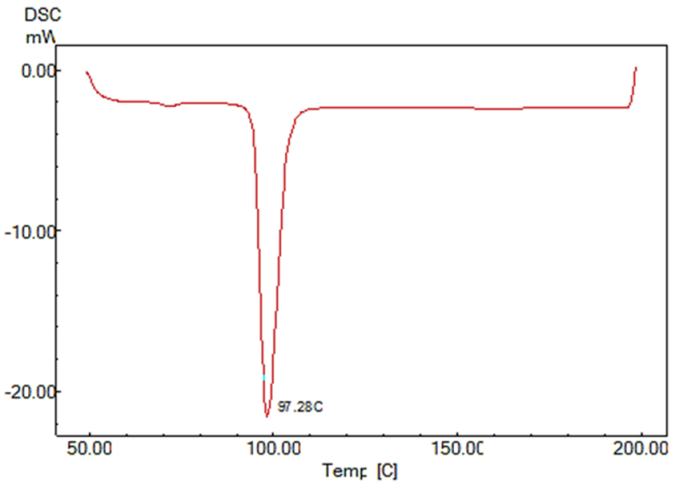

Fig. 1: Thermal analysis of ketoprofen

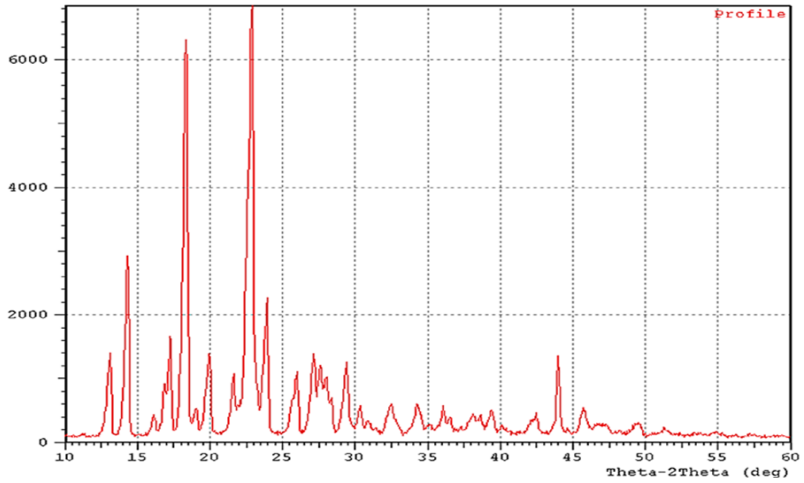

Fig. 2: XRD of pure ketoprofen

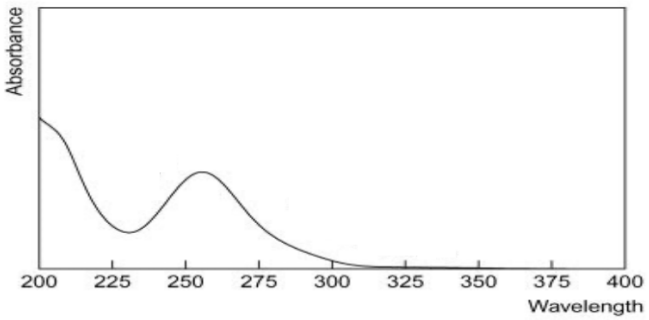

Fig. 3: UV spectra of KET solution at 6 µg/ml

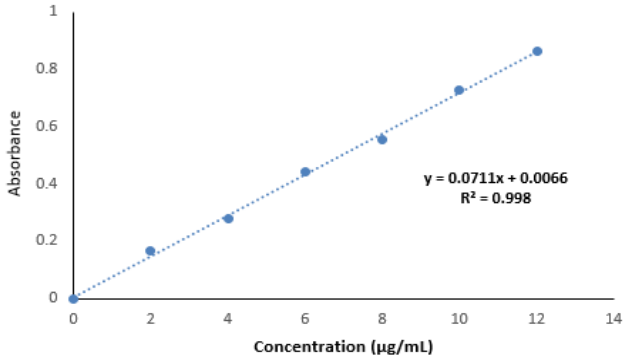

Fig. 4: Calibration curve of KET (n=3)

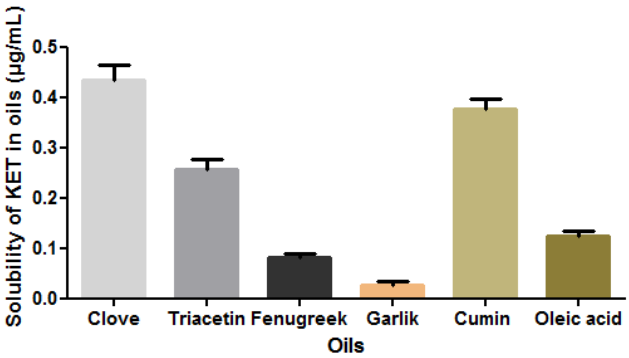

Fig. 5: Solubility of KET in various oils. Error bars represent the standard deviation of replicates (n = 3)

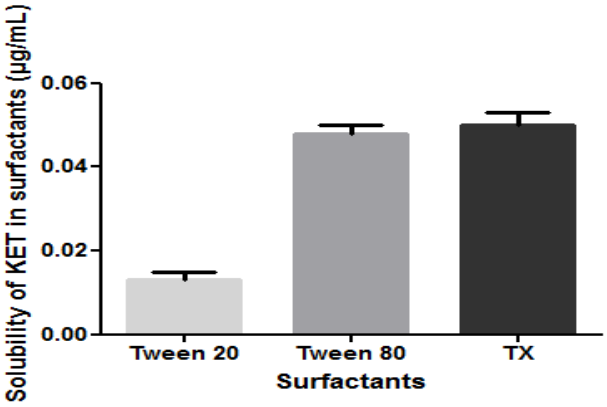

Fig. 6: Solubility of KET in various surfactants. Error bars indicate the standard deviation of replicates (n = 3)

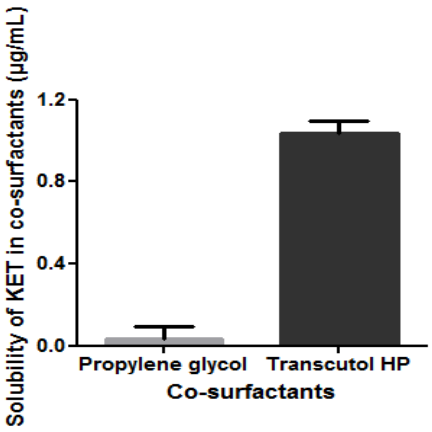

Fig. 7: Solubility of KET in different Co-surfactants. Error bars represent the standard deviation of replicates (n = 3)

Construction of phase diagrams

Based on the results of ketoprofen solubility in different oils, Smix (surfactant/co-surfactant), clove oil was used as oil phase, tween 80 as surfactant and transcutol HP as co-surfactants and water (components of the pseudo-ternary phase triangle). By volume measurements of nano-emulsion components of Smix (Tn80-Hp) oil and water, the results were shown in fig. 8, 9, 10, 11. The optimal formal was obtained using clove oil, tween 80, (Smix 3:1), and DDW, which shows the largest stable emulsion area.

Evaluation of self-emulsification time

Seven formulations of prepared KET-loaded nanoemulsion were studied with respect to the clarity of nanoemulsion. Table 2 shows the emulsification time and the visual appearance of each tested formula.

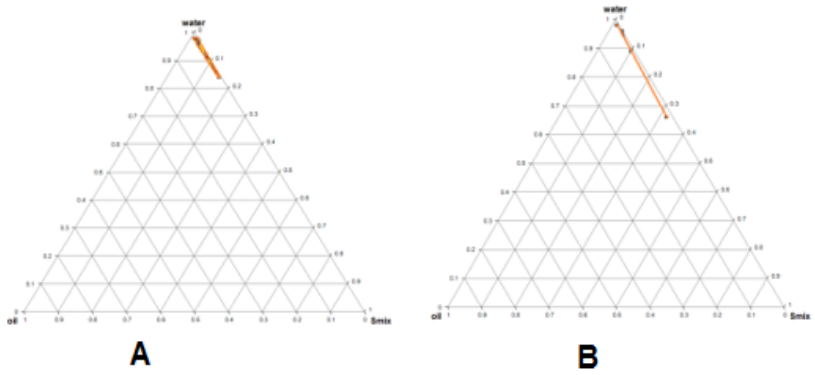

Fig. 8: Pseudo ternary phase diagram of clove oil, tween 80 and water. A: Smix 1:1 B: Smix 1:2

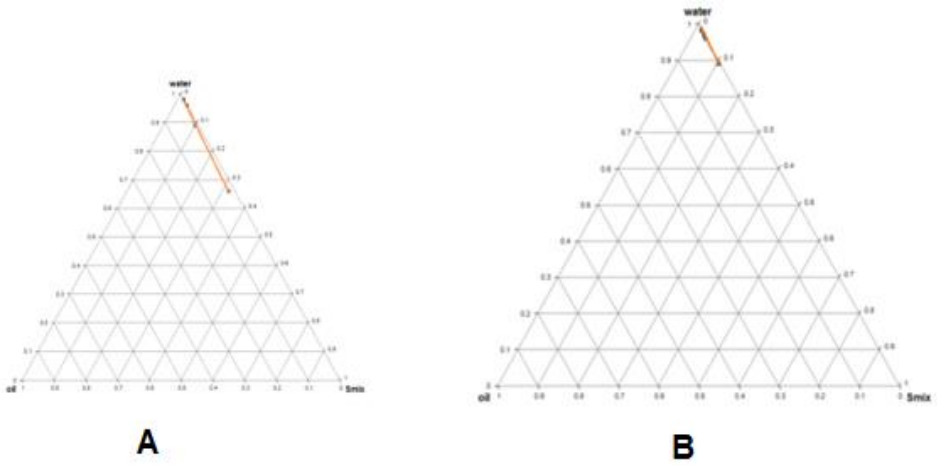

Fig. 9: Pseudo ternary phase diagram of clove oil, tween 80 and water. A: Smix 1:3 B: Smix 1:4

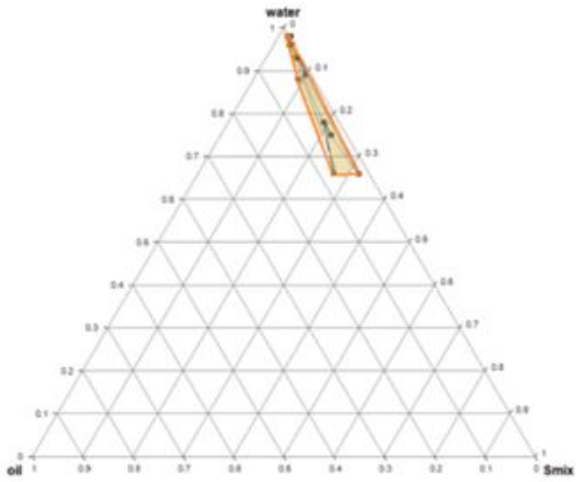

Fig. 10: Pseudo ternary phase diagram of clove oil, tween 80 and water. Smix 2:1

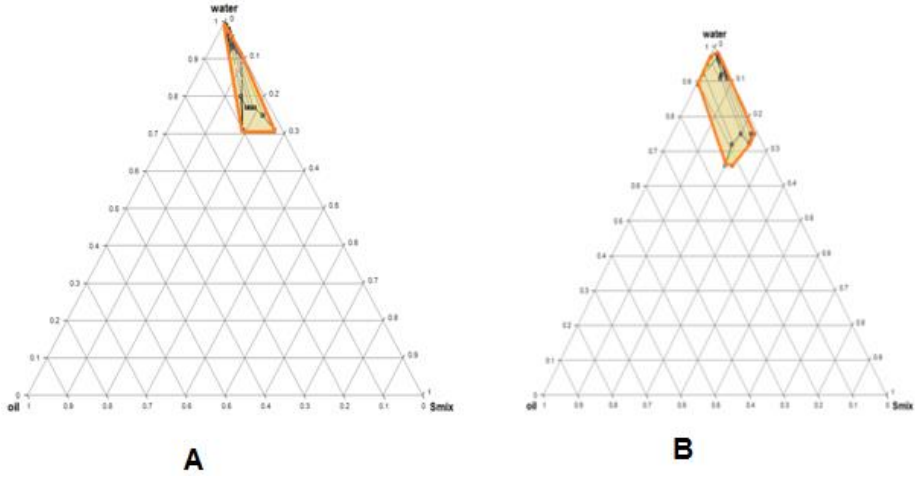

Fig. 11: Pseudo ternary phase diagram of clove oil, tween 80 and water. A: Smix 3:1 B: Smix 4:1

Table 2: Emulsification time and visual appearance of selected formulations

Formula code	Clove oil %	S: cosur mix ratio	Emulsification time (second)	Appearance
F1	10%	1:1	10	clear
F1	20%	1:1	16	Turbid
F1	30%	1:1	18	Turbid
F2	10%	1:2	12	clear
F2	20%	1:2	12	Turbid
F2	30%	1:2	13	Turbid
F3	10%	1:3	12	clear
F3	20%	1:3	14	Turbid
F3	10%	1:3	15	Turbid
F4	10%	1:4	12	clear
F4	20%	1:4	14	Turbid
F4	30%	1:4	18	turbid
F5	10%	2:1	10	Very clear
F5	20%	2:1	12	Very clear
F5	30%	2:1	15	Turbid
F6	10%	3:1	10	Very clear
F6	20%	3:1	14	Very clear
F6	30%	3:1	15	Turbid
F7	10%	4:1	20	Very clear
F7	20%	4:1	20	Very clear
F7	30%	4:1	20	Turbid

Table 3: Thermodynamic stability test of selected SEDDS formulations

Formula code	Centrifugation test	Heating-cooling cycles test	Freeze-thawing cycles test
F1	Pass	Pass	Pass
F2	Pass	Pass	Pass
F3	Pass	Pass	Pass
F4	Pass	Pass	Pass
F5	Pass	Pass	Pass
F6	Pass	Pass	Pass
F7	Pass	Pass	Pass
F8	Pass	Pass	Pass
F9	Pass	Pass	Pass
F10	Pass	Pass	Pass

Dilution study

All the formulations showed stability and no phase separation or drug precipitation when diluted with an excess of water, 0.1 N HCl and phosphate buffer (pH 6.8) after 24 h storage [22].

Evaluation of thermodynamic stability

Thermodynamic study was conducted to indicate and exclude the unstable formula. From the data shown in table 3, all the prepared nanoemulsion formulations were passed the thermodynamic test with no phase separation [23].

Measurement of droplet size, size distribution and zeta potential

Droplet size plays a vital role in the self-emulsification process since it affects the rate of drug absorption and, consequently bioavailability [24]. The impact of formulations on droplet size was shown in table 4. When the ratio of surfactant to co-surfactant increases from 1:1 to 3:1, the droplet size is decreased from 200 nm to 105 nm. It is noted that the droplet size of KET-nanoemulsion was decreased by increasing surfactant concentration. This decrease in droplet size may be attributed to the role of surfactant in stabilising

the emulsion where a rigid film of surfactant is formed at the oil/water interface [25]. With respect to the effect of oil concentration, droplet size increased with increasing oil concentration, where the size was increased from 120 nm in F5 to 193 nm in F6 and from 105 nm in F7 to 154 nm in F8 when the concentration of oil increased from 10 to 20%. This increase in oil concentration may cause an increase in the viscosity of the oil-drug phase. This increase in viscosity might affect the homogenisation efficiency during the initial step of emulsification and consequently, a larger droplet size was obtained [26]. Fig. 12 shows the size of F7.

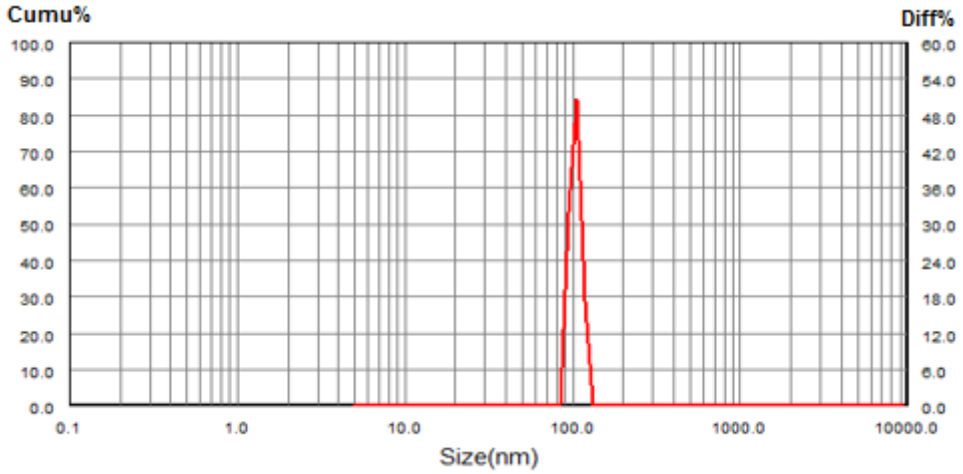

Fig. 12: Droplet size distribution of selected nanoemulsion F7 (n=3)

Overall charges gained by particles in a dispersion medium is measured using zeta potential, which plays an essential role in the evaluation of the stability of colloidal dispersion. A repulsion will occur between particles if the system possesses a high negative or positive value of zeta potential [15]. Based on the thumb rule, excellent stability is obtained when absolute ZP values ranged from ≤-60 mV to ≥ 60 mV. Value in the range (-20 mV to+20 mV) gives only short-term stability while values in the range of ≤-30 mV to ≥+20 mV provide good stability. On the other hand, ZP values ranged from-5 mV to+5 mV show fast aggregation. In the case of higher or large molecular weight stabilizers, which act mainly by steric stabilization, the value of zeta potential of 20mV or lower shows an efficient stabilization [27]. The magnitude of zeta potential of optimal formulation F7 was-26.21 mV±0.08 (n=3) (fig. 13).

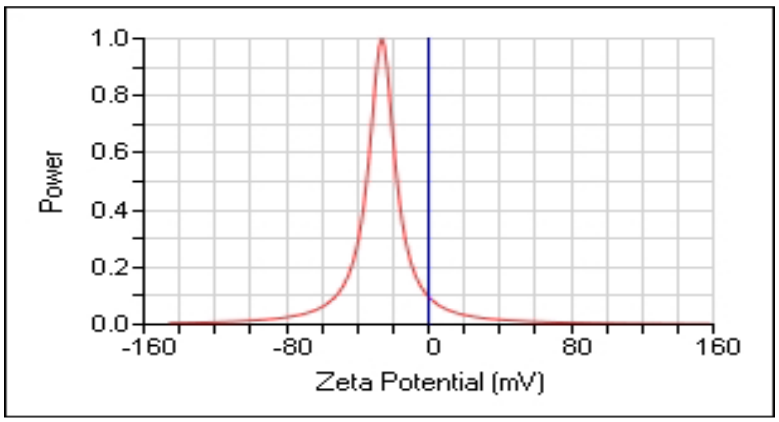

Fig. 13: Zeta potential of optimal formulation (F7) (n=3)

Table 4: Droplet size of Ketoprofen SEDDS formulations

Formula code	Droplet size (nm)	PDI
F1	200±6.22	0.010±0.0.02
F2	225±4.08	0.009±0.01
F3	223±5.82	0.009±0.04
F4	235±3.43	0.016±0.06
F5	120±2.08	0.012±0.01
F6	193±6.39	0.008±0.05
F7	105±3.55	0.010±0.03
F8	154±2.85	0.013±0.04
F9	135±3.34	0.043±0.02
F10	158±4.28	0.017±0.03

Data are represented as mean±SD (n=3)

In vitro dissolution study

In vitro release study was carried out to investigate the effect of oil, surfactant and co-surfactants on the release profile of Ketoprofen obtained from prepared KET SEDDS formulations. Cumulative % drug release patterns of KET SEDDS were shown in fig. 14. An initial fast release of Ketoprofen was obtained from all prepared nanoemulsion formulations within the first 10 min and the release pattern was continued for 60 min. In fig. 14, it was observed that the drug release from formulations F5, F6, F7, F8, F9 and F10 was higher than that of F1, F2, F3 and F4. Such a rapid release behaviour obtained in F5–F10 may be attributed to the high surfactant to co-surfactant ration contained in these formulations, which produces a spontaneous formation of nanoemulsion with fine droplet size. Consequently, a nanosized droplet produces more surface area for the drug to be released from the system into dissolution media [28, 29]. Among F5-F10 formulas, F7 and F9 exhibited a cumulative KET release of 100% and 85.36% after 60 min, respectively in comparison to F8 and F10 where the cumulative KET release was 82.145 and 58.97%, respectively. This may be related to the concentration of oil in these formulations. The percentage of oil in both F7 and F8 was 10%, while in F8 and F10 was 20%. Based on Einstein-Stokes law for a driven process of diffusion, the prolonged release profile of lipid system could be inversely affected by the viscosity of the lipid. Thus, increasing the percentage of oil in F8 and f10 to 20% might result in higher internal viscosity of oil droplets and a slower rate of release [30].

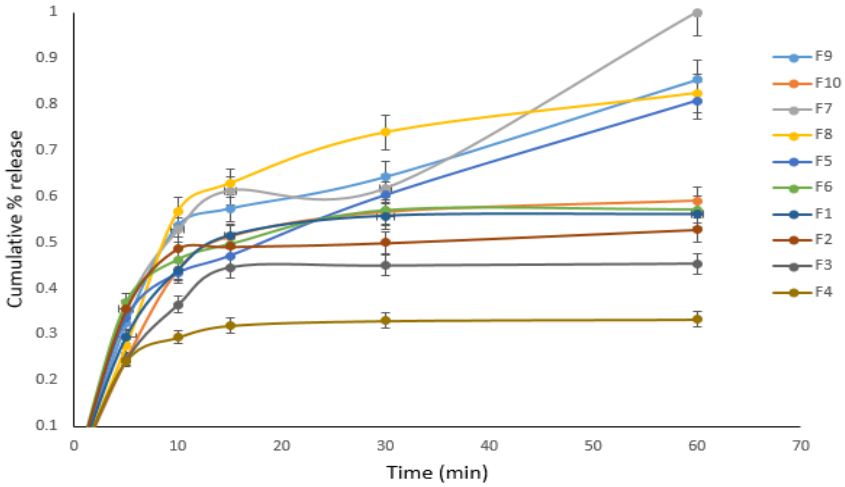

Fig. 14: *In vitro* dissolution profiles of KET nanoemulsion formulation. Error bars indicate the standard deviation of replicates (n = 3)

CONCLUSION

In the present work, Ketoprofen, a poorly water-soluble drug was formulated into nanoemulsion to enhance its dissolution and improve its absorption. nanoemulsion of KET was formulated and optimized using parameters such as droplet size, size distribution, zeta potential and *in vitro* release data. Optimal formula of nanoemulsion was composed of clove as the oil phase, Tween 80 as surfactant and Transcutol PH as co-surfactant. F7 (10% oil phase, 3:1 surfactant to co-surfactant ratio) revealed a droplet size of 105 nm and zeta potential value of-26.21 mV. *In vitro* release study demonstrated that the drug release from formulations F5, F6, F7, F8, F9 and F10 was higher than that of F1, F2, F3 and F4.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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