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Original Article

FORMULATION AND *IN VITRO* EVALUATION OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM OF QUERCETIN FOR ENHANCEMENT OF ORAL BIOAVAILABILITY

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ABSTRACT

Objective: The study aims to develop a Self-nanoemulsifying drug delivery system (SNEDDS) of Quercetin to enhance its oral bioavailability.

Methods: In the present study, Quercetin was formulated into SNEDDS using various oils, surfactants, and co-surfactants. The developed formulations were subjected to various studies like drug content analysis, droplet size and thermodynamic stability, and *in vitro* drug release studies.

Results: From the screening of oils, surfactant and cosurfactant, the combination of Triacetin as oil phase, Tween 20 as surfactant and Ethanol as co-surfactant was selected for the development of SNEDDS of Quercetin. The composition of the formulation was optimized using pseudo ternary phase diagram. The optimized formulation has been evaluated and found to have good physical stability and improved *in vitro* drug release.

Conclusion: A stable SNEDDS of Quercetin was developed, and results indicated substantial enhancement in the dissolution of the drug when formulated as a self-nano emulsifying drug delivery system, indicating its potential to enhance oral solubility and bioavailability of the drug.

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

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INTRODUCTION

Quercetin (fig. 1) is a polyphenolic flavonoid, which is the safe, most abundant, and commonly ingested dietary phytochemical which possess a wide spectrum of pharmacological action, mainly antiviral, antidiabetic, anti-inflammatory, neuroprotection and anti-proliferative [1]. However, clinical applications of quercetin are limited due to its hydrophobicity and poor gastrointestinal absorption [2]. Several attempts have been made to improve the poor bioavailability of Quercetin, including a Self-emulsifying drug delivery system (SEDDS) [3, 4].

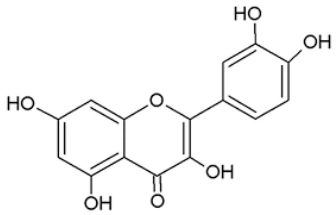


Fig. 1: Structure of quercetin

Self-emulsifying drug delivery system (SEDDS) formulation are isotropic mixture of an oil, surfactant, co-surfactant and drug, that has the ability to form emulsion with water under gentle agitation as in the gastrointestinal tract. This spontaneous emulsion formation *in vivo* presents the drug in the solubilized form and the small particle size of the droplets provide a large interfacial area, which promote higher rate and extent of absorption [5, 6]. Self-Nano Emulsifying Drug Delivery System (SNEDDS) are much more stabler form of SEDDS that have received particular attention as a means of enhancing oral bioavailability of poorly absorbed drug [7].

In the present study, Quercetin was formulated into Self-Nano Emulsifying Drug Delivery System (SNEDDS) to overcome its poor bioavailability and evaluated *in vitro*.

MATERIALS AND METHODS

Materials

Quercetin was purchased from TCI chemicals (India), Pvt. Ltd. All the other chemicals and solvents used in the study were of analytical grade.

Methodology

Solubility study of quercetin in different oils, surfactant, and co-surfactant

For determination of the solubility of Quercetin in various oils, surfactant and co-surfactant, excess amount of drug was suspended separately in 1 ml of each solvent (oil/surfactant/co-surfactant) at room temperature in tightly closed centrifuge tubes and shaken in a bath shaker (NSW-128, Remi Equipments, Mumbai, India) for 24 h. The samples were then centrifuged, and the supernatant was estimated for drug content spectrophotometrically using validated method [8].

Preliminary screening of oils, surfactants, and co-surfactant

The mixtures containing selected oils and surfactants were gradually heated at 50 °C for homogenization of the components. Each mixture was then diluted with distilled water to 100 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield homogenous emulsion. Emulsions were allowed to stand for 2 h and their % transmittance was evaluated at 638 nm by UV-Visible spectrophotometer (UV1800, Shimadzu, Japan) using distilled water as a blank. Emulsions were furthermore observed visually for any turbidity or phase separation [9].

Solubility of quercetin in the screened mixture

The selected oil phase and surfactant were used for further screening of the different co-surfactants for their drug solubility ability. An estimated amount of Quercetin was added in the solution mixture of optimized oil and surfactant along with the selected co-surfactant. Each solvent was kept at room temperature in tightly closed culture tubes and shaken in a bath shaker for 24 h. The

samples were then centrifuged, and the supernatant was estimated for solubilized drug [10].

Pseudo ternary phase diagram

Phase diagrams involve plotting the three components oil (triacetin), surfactant: co-surfactant (S_{mix} i.e., tween 20: ethanol) and water content, each of them representing an apex of triangle. The required amounts of the components (oil and Smix) were weighed accurately and then sonicated for 3 min. The mixture was then gently heated at 45–50 °C and vortex to form a homogenous mixture. To this mixture, distilled water was added drop by drop until a transparent solution was formed. The surfactant and co-surfactant (Smix) were varied in mass ratios 1:1, 1:2, 1:3, 2:1 and 3:1. Pseudo ternary mixtures were formed in these ratios and then the quantity of water forming transparent solution was plotted with other components in the pseudo-ternary phase diagram [11].

Preparation of liquid SNEDDS

Different formulations were carefully chosen from the zone of nanoemulsions of each constructed phase diagram, based on objective that the oil phase concentration should be such that it would be capable to dissolve 0.05% w/v of Quercetin. Quercetin was dissolved in two different concentrations one being 0.015% w/v and 0.05% w/v in oil, the mixture of surfactant and co-surfactant was mixed in oil phase in appropriate quantity while deionized water was further added in dropwise way with constant vortexing until the formation of a clear transparent monophasic liquid state.

Evaluation of SNEDDS formulation

Percentage drug content

The selected formulations were evaluated for drug content. Then the formulation was diluted with methanol and absorbance was measured at 374 nm by UV Spectrophotometer [12].

pH of SNEDDS

SNEDDS (100 µl) was dissolved in 5 ml of distilled water. pH of the nanoemulsion was measured by using pH meter (ST3100M, Ohaus, USA)at room temperature. pH of SNEDDS was measured before dilution and after dilution with aqueous phase [13].

Self-Emulsification time and robustness to dilution

To determine the emulsification time (time needed to reach the emulsified and homogeneous mixture, upon dilution), formulation containing Quercetin (0.015% w/v and 0.05% w/v) was added to 100 ml of 0.1N HCl, 100 ml of Phosphate Buffer pH 6.8 and 100 ml of distilled water at 37 °C with gentle agitation using a magnetic stirrer (.100MHPS0515000, Remi Equipments, Mumbai, India). d The formulation was assessed visually according to the rate of emulsification and the final appearance of the emulsion [14].

Note: Based on the above evaluation parameters optimized formulations were selected for further evaluation

Thermodynamic stability studies

Optimized formulation was subjected to thermodynamic stability studies to access any phase separation and stability of the formed nanoemulsion [15].

Centrifugation study

The formulation was centrifuged in a centrifuge (CPR-30-PLUS, Remi Equipments, Mumbai, India) at 18000 rpm for 30 min. The resultant formulation was then checked for any instability problem, such as phase separation, creaming, or cracking.

Heating and cooling cycle

The liquid SNEDDS formulations were subjected to a heating-cooling test using six refrigerator cycles at 45 °C and 4 °C temperatures separately for 48 h in an incubator (Remi, Mumbai, India). Afterward, it was assessed for phase separation.

Cloud point measurement

The cloud point temperature of the diluted formulation was determined by gradual heating on a water bath and the temperature at which cloudiness appears was denoted using the thermometer. The formulation was diluted with distilled water in the ratio of 1:100. The diluted samples were placed in a water bath and its temperature was increased gradually. Cloud point was determined as the temperature at which there was a sudden appearance of cloudiness [16].

Viscosity studies

The viscosity of the optimized formulation was measured using small sample adapter of Brookfield viscometer (ViscoQC100, Anton Paar, Gurugram, India) at 12 rpm at room temperature (25±1 °C), repeated in triplicate [17].

Particle size

The particle size of the selected formulation was determined by using particle size analyzer (Litesizer 500, Anton Paar, Gurugram, India). The measurements were performed at 25 °C at a fixed angle of 90°. Aliquots of the formulation, serially diluted with purified water, were employed to assess the particle size using a particle size analyzer [18].

Transmission electron microscopy (TEM)

Transmission electron microscopy (H-600, Hitachi, Japan) was employed to study the morphology of the resulting nanoemulsion. Prior to the analysis, the SNEDDS samples were diluted 1000 times with water to form an emulsion, stained with 2% (w/v) phosphotungstic acid for 30 s and placed on 400-mesh copper grids with films for observation [19].

***In vitro* drug release**

The relative *in vitro* dissolution behavior of quercetin from pure quercetin and SNEDDS filled capsule in 0.1 N hydrochloric acid (900 ml; pH 1.2; 37±0.5 ℃) was assessed using USP type I apparatus-basket type (DS8000, Labindia Ltd. Mumbai, India)at a rotation speed of 50 rpm. At predetermined time points (0, 5, 10, 15, 20, 25 and 30 min), an aliquot of 5 ml was withdrawn with equal volumes of fresh dissolution medium replacements to maintain the medium volume constant. All the samples were filtered, diluted and the concentration of quercetin dissolved was estimated spectro-photometrically at 374 nm.

RESULTS AND DISCUSSION

Solubility study of quercetin in different oils, surfactant, and co-surfactant

Solubility study of quercetin in different oils (fig. 2), surfactants (fig. 3), and co-surfactants (fig. 4) were determined.

In case of oils**,** the solubility of Quercetin was found in Capmul MCM>Triacetin>Labrafil 2125 CS>Acconon MCB-2>Maisine CC>Labrafac MCM 1944 CS and was found to be more than 2 mg/ml.

In case of Surfactants, the solubility of Quercetin was found in maximum in the case of Tween 20, followed by Labrasol ranging from 4.232±0.005 to 27.078±0.133 mg/ml.

In case of Co-surfactants, the solubility of Quercetin was found in maximum in case of Ethanol, followed by PEG 400 and PEG 200 ranging from 6.229±0.002 to 20.000±0.030 mg/ml.

Preliminary screening of oils, surfactants and co-surfactant

Different combinations (F1 to F15) of selected oils and surfactants (ratio 3:2) were subjected to an emulsification efficiency study to select which one tends to have the maximum soluble content of quercetin. It was found (fig. 5) that the F4 with oil phase as Triacetin and surfactant phase as Tween 20 and F8 with oil phase as Acconon MCB-2 and surfactant phase as Tween 80 showed maximum transmittance without any evident turbidity and phase separation. The provided two combinations were further subjected to screening of co-surfactant study.

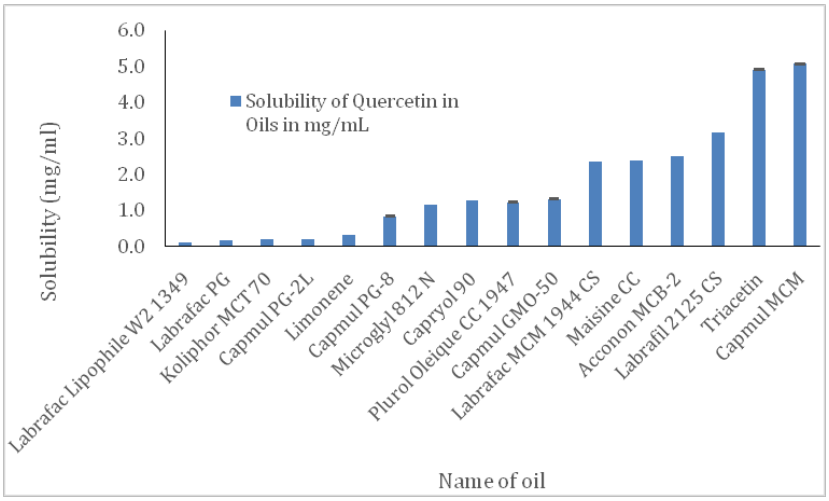


Fig. 2: Solubility profile of quercetin in different oils

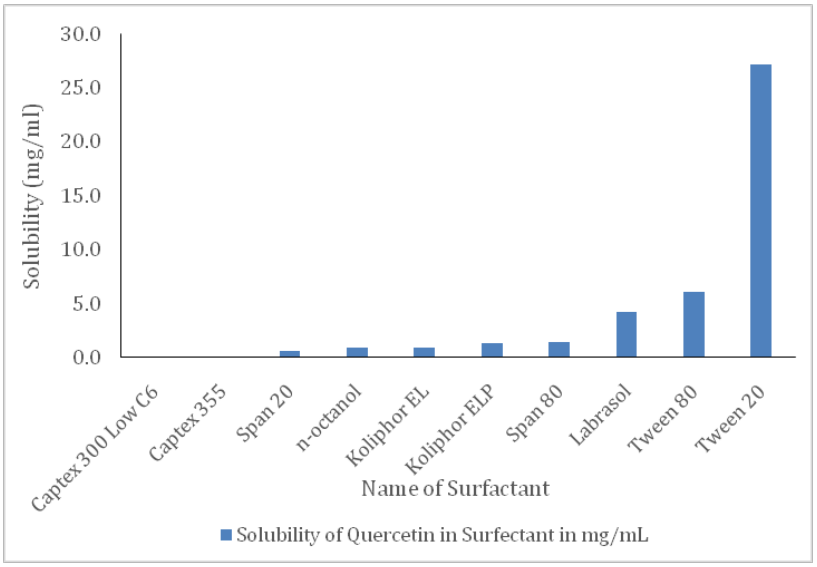


Fig. 3: Solubility profile of quercetin in different surfactants

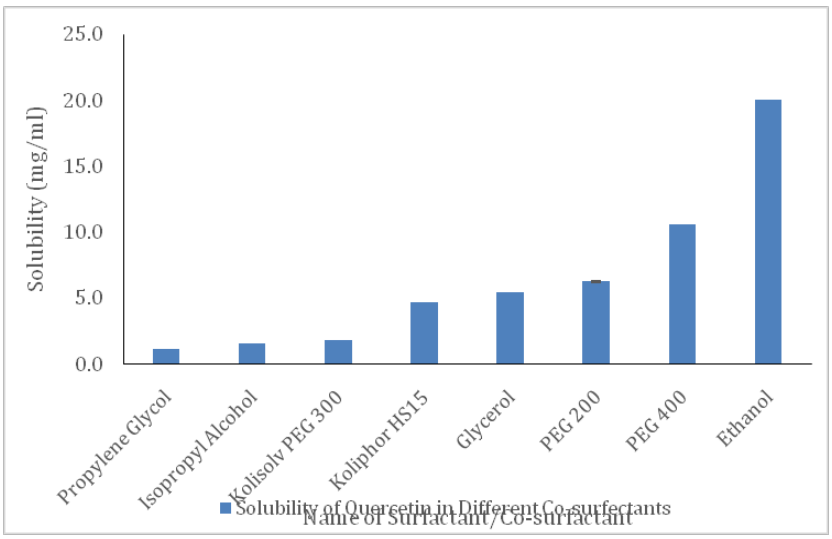


Fig. 4: Solubility profile of quercetin in different co-surfactants

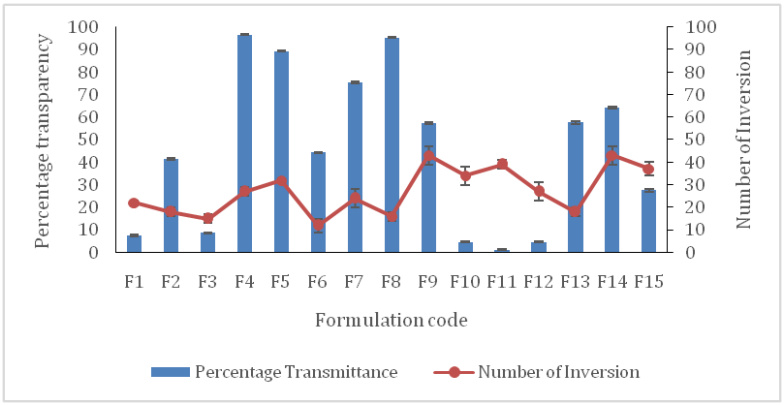


Fig. 5: Transmittance study of different oils and surfactants

The mixture were further subjected to emulsification study with the addition of different co-surfactant (PEG 200, Koliphor HS15, PEG 400, Glycerol and Ethanol) with each of the selected mixture in the ratio oil: surfactant: co-surfactant ie 3:2:2 to produce formulations F16 to F25. It was found that the transmittance (fig. 6) was to be maximum in case of F20, where Ethanol was used as a co-surfactant with Triacetin (oil) and tween 20 (surfactant). Furthermore, it didn't show any evident turbidity and phase separation.

Solubility of quercetin in screened mixture

When around 0.05% w/v of the drug was added to the mixture solution, the solubility was found to be was found to be 33.31±0.457 mg/ml. From the screening of surfactant and cosurfactant the combination Triacetin as oil phase, Tween 20 as surfactant and Ethanol as co-surfactant was selected for the preparation of pseudo ternary phase diagram.

Pseudo ternary phase diagram

In this provided combination of oil, surfactant and co-surfactant, formulations as shown in the shaded portion of the pseudo ternary phase diagrams (fig. 7, fig. 8, fig. 9, fig. 10, fig. 11) was transparent on addition of water. While the remaining formulation were found to be turbid upon the addition of water up to the amount of 5 ml. The above-mentioned formulations remain transparent even after 24 h of water addition. However, the ones having turbid appearance doesn't exhibit any change even after 24 h of water addition.

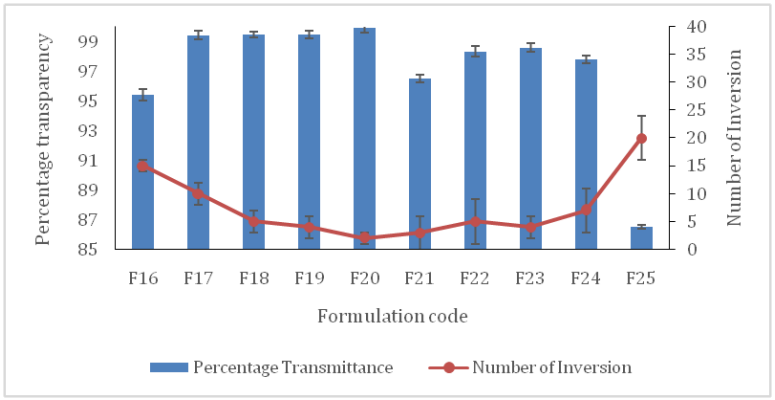


Fig. 6: Transmittance study of different oils, surfactants and co-surfactants

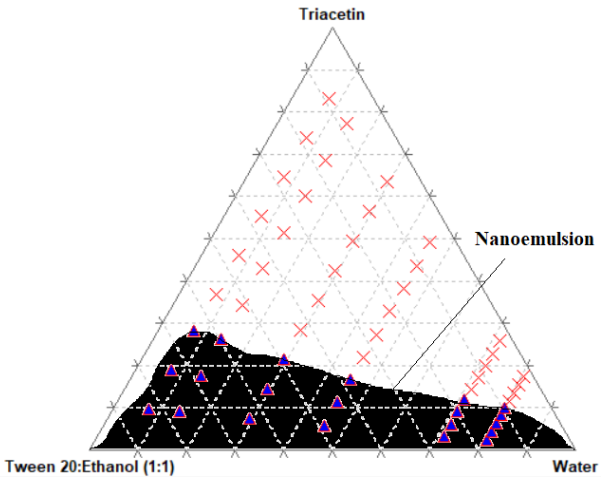


Fig. 7: Pseudo ternary phase diagram of combination of oil, smix (1:1) and water

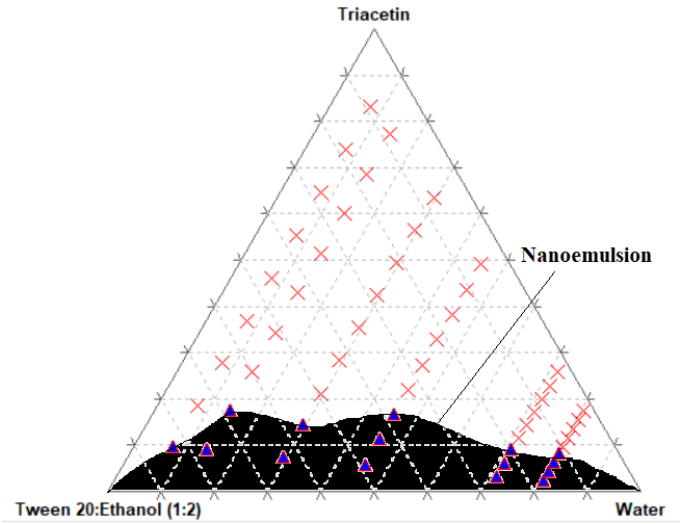


Fig. 8: Pseudo ternary phase diagram of a combination of oil, surfactant: cosurfactant (1:2) and water

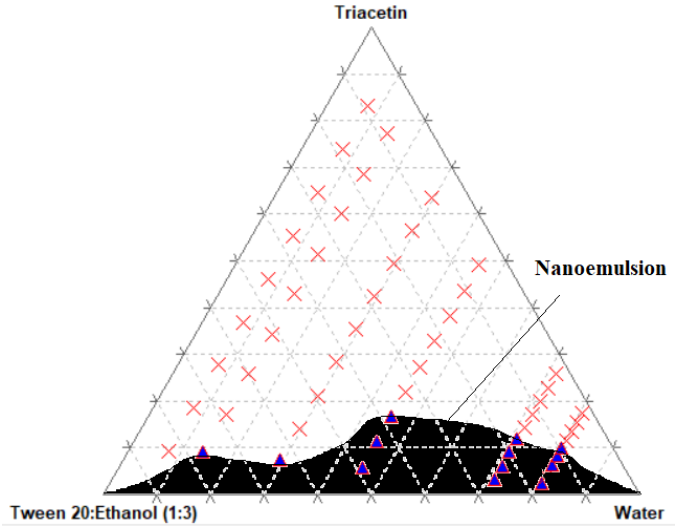


Fig. 9: Pseudo ternary phase diagram of a combination of oil, surfactant: co-surfactant (1:3) and water

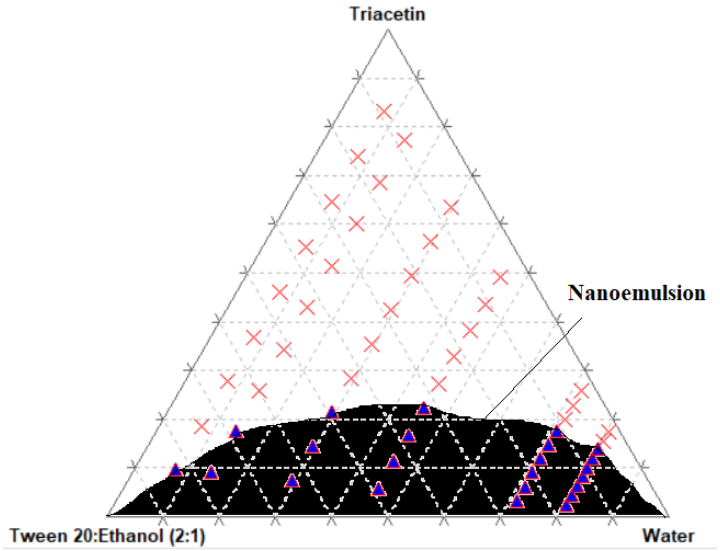


Fig. 10: Pseudo ternary phase diagram of a combination of oil, smix (2:1) and water

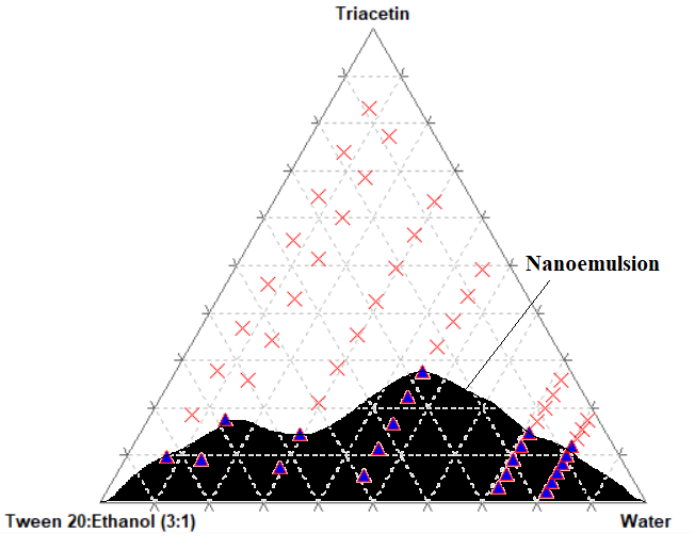


Fig. 11: Pseudo ternary phase diagram of combination of Oil, Smix (3:1) and water

Preparation of liquid SNEDDS

Based on the results of the pseudoternary phase diagram, various formulations of SNEDDS of were prepared by varying the concentration of oil, surfactant and cosurfactant as in table 1.

Evaluation of SNEDDS formulation

Percentage drug content of SNEDDS

The prepared formulation was subjected to percentage drug content analysis. From the fig. 12 it can be inferred that most of the formulations were having high drug content, comprising about 97.98±0.105 to 100.88±0.457 percent of Quercetin loaded into the formulation.

pH of liquid SNEDDS containing quercetin

On pH study of selected Liquid SNEDDS containing Quercetin, pH of all the formulations was found to be in a range of 6.05±0.040 to 6.86±0.015.

Self-emulsification time and robustness to dilution

Initially, the drug incorporated for the preparation of nanoemulsion was 0.05% w/v of the emulsion and precipitation was witnessed in all these formulation with 0.1N HCl and Phosphate Buffer pH 6.8 solution. However, upon reduction of the fed Quercetin to 0.015% w/v, all the formulation form nanoemulsion within 8 seconds upon diluting it into 0.1N HCl and Phosphate Buffer pH 6.8 solution (table 2). However, as far as the stable homogeneity and transparency is concerned, the formulation NE4, NE10 and NE22 was found to have clear transparent appearance even after 24 h. In case of distilled water, all the formulations were found to have a clear, yellowish transparent appearance.

Thermodynamic stability studies

Centrifugation study

Upon centrifugation study, all three selected SNEDDS formulations (NE4, NE10 and NE22) were found to be stable after centrifugation. No sign of phase separation was seen in the formulations.

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

Nanoemulsion/ SNEDDS	Nanoemulsions composition (%, w/w)			S_{mix} ratio
	Oil	Surfactant	Co-surfactant	
	Triacetin (%)	Tween-20 (%)	Ethanol (%)	
NE1	20.18	39.91	39.91	01:01
NE2	30.01	34.99	34.99	01:01
NE3	33.25	33.37	33.37	01:01
NE4	40.71	29.65	29.65	01:01
NE5	50.74	24.63	24.63	01:01
NE6	20.3	26.57	53.14	01:02
NE7	36.85	21.05	42.1	01:02
NE8	29	23.67	47.34	01:02
NE9	40.05	19.98	39.97	01:02
NE10	20.1	19.97	59.92	01:03
NE11	30.01	17.5	52.49	01:03
NE12	39.65	15.09	45.26	01:03
NE13	49.25	12.69	38.07	01:03
NE14	20.41	53.06	26.53	02:01
NE15	30.09	46.61	23.3	02:01
NE16	40.29	39.81	19.9	02:01
NE17	50.79	32.81	16.4	02:01
NE18	60.14	26.58	13.29	02:01
NE19	69.59	20.27	10.14	02:01
NE20	20.34	59.75	19.92	03:01
NE21	30.03	52.48	17.49	03:01
NE22	39.97	45.02	15.01	03:01
NE23	50.29	37.28	12.43	03:01

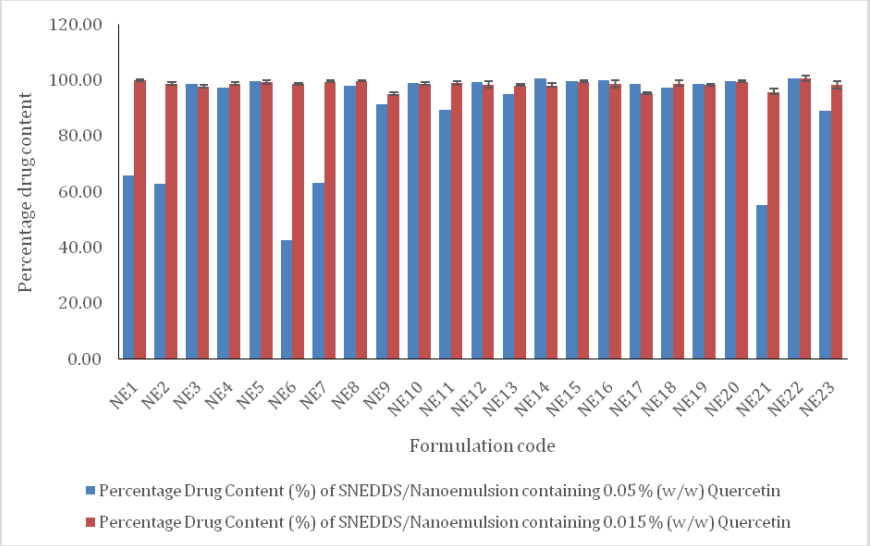


Fig. 12: Percentage drug content of liquid SNEDDS containing quercetin

Table 2: Self emulsification and robustness to dilution study of SNEDDS (Quercetin 0.015% w/v)

Formulation code	Appearance of homogeneous, clear, yellowish transparent solution without precipitation					
	In 100 ml 0.1N HCl			In 100 ml 6.8 phosphate buffer		
	Emulsification time	After dilution	After 24 H	Emulsification time	After dilution	After 24 H
NE1	Within 5-6 seconds	✓	X	Within 4-5 seconds	✓	✓
NE2	Within 7-8 seconds	X	X	Within 5-6 seconds	X	X
NE3	Within 3 seconds	✓	X	Within 3 seconds	✓	X
NE4	Within 1-2 seconds	✓	✓	Within 1-2 seconds	✓	✓
NE5	Within 2-3 seconds	✓	X	Within 5-6 seconds	X	X
NE6	Within 5-6 seconds	✓	X	Within 4-5 seconds	✓	✓
NE7	Within 8 seconds	✓	X	Within 4-5 seconds	✓	X
NE8	Within 3 seconds	✓	✓	Within 5-6 seconds	X	X
NE9	Within 7-8 seconds	X	X	Within 5-6 seconds	X	X
NE10	Within 1-2 seconds	✓	✓	Within 3 seconds	✓	✓
NE11	Within 8 seconds	✓	X	Within 5-6 seconds	✓	✓
NE12	Within 2-3 seconds	✓	X	Within 4-5 seconds	✓	✓
NE13	Within 7-8 seconds	✓	X	Within 4-5 seconds	✓	X
NE14	Within 5-6 seconds	✓	X	Within 5-6 seconds	X	X
NE15	Within 5-6 seconds	✓	X	Within 5-6 seconds	X	X
NE16	Within 7-8 seconds	✓	X	Within 7-8 seconds	X	X
NE17	Within 8 seconds	X	X	Within 3 seconds	X	X
NE18	Within 5-6 seconds	✓	X	Within 5-6 seconds	X	X
NE19	Within 3 seconds	✓	X	Within 3 seconds	✓	✓
NE20	Within 8 seconds	✓	X	Within 4-5 seconds	✓	X
NE21	Within 7-8 seconds	X	X	Within 7-8 seconds	X	X
NE22	Within 1-2 seconds	✓	✓	Within 3 seconds	✓	✓
NE23	Within 5-6 seconds	✓	X	Within 4-5 seconds	✓	✓

✓-passed, X-failed

Table 3: Centrifugation study of liquid SNEDDS containing quercetin

S. No.	Formulation code	Appearance
1.	NE4	Homogenous, no phase separation
2.	NE10	Homogenous, no phase separation
3.	NE22	Homogenous, no phase separation

Table 4: Heating and cooling cycle of liquid SNEDDS containing quercetin

S. No.	Formulation code	Heating (40 °C)	Cooling (4 °C)
1.	NE4	Homogenous, no phase separation	Homogenous, no phase separation
2.	NE10	Homogenous, no phase separation	Homogenous, no phase separation
3.	NE22	Homogenous, no phase separation	Homogenous, no phase separation

The nanoemulsions formed from the optimized SNEDDS formulations are found to be thermodynamically stable systems without phase separation, creaming and cracking.

Heating and cooling cycle

The optimized SNEDDS examined for centrifugation and heating-cooling cycle, passed these tests and no phase separation, creaming or cracking were observed.

Cloud point measurement

Estimation of cloud points is an important factor for the stability of the self-emulsifying formulation. The cloud point is the temperature above which dehydration of self-emulsifying ingredients occurs and turns a clear dispersion to a cloudy one which in turn may affect drug absorption. Hence, cloud point of the self-emulsifying formulation should be above body temperature (37 °C). The cloud point of NE4, NE10 and NE22 indicated the formed SNEDDS at the physiological temperature will be a stable one.

Table 5: Cloud point measurement of liquid SNEDDS containing quercetin

S. No.	Formulation code	Cloud point
1.	NE4	59.83±1.607
2.	NE10	63.17±0.764
3.	NE22	67.07±1.401

Viscosity studies

Estimation of viscosity was carried out of the enlisted formulations and was found to be in the range of 187.67±2.309 to 275.67±1.528 cP. Also, the lower viscosity of SNEDDS is mainly due to the smaller droplet size.

Table 6: Viscosity of the liquid SNEDDS containing quercetin

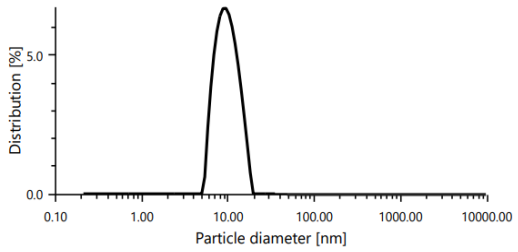
S. No.	Formulation code	Viscosity (in cP)
1.	NE4	187.67±2.309
2.	NE10	275.67±1.528
3.	NE22	203.87±1.629

Determination of particle size

Fig. 13-15, shows the particle size and PDI of optimized SNEDDS formulation

Transmission electron microscopy of SNEDDS

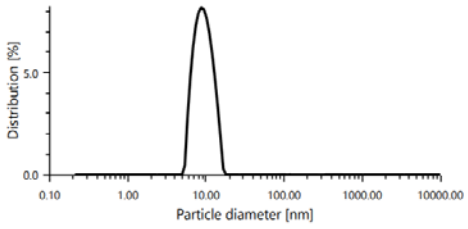
As shown in the TEM photograph (fig. 16), the diluted preparation (nanoemulsion) appears spherical and homogeneous with a large population of the smaller droplet in the size range of less than 125 nm, which is consistent with the distribution data obtained from particle size measurement.



Results

Hydrodynamic diameter	11.96 nm	**Mean intensity**	288.2 kcounts/s
Polydispersity index	22.1 %	**Absolute intensity**	1296.2 kcounts/s
Diffusion Coefficient	41.0 µm²/s	**Intercept g1²**	0.8670
Transmittance	80.6 %	**Baseline**	1.092

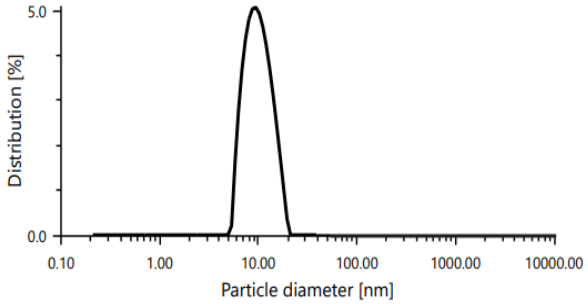
Fig. 13: Graph of particle size of NE4 formulation



Results

Hydrodynamic diameter	83.06 nm	**Mean intensity**	292.5 kcounts/s
Polydispersity index	23.5 %	**Absolute intensity**	924.6 kcounts/s
Diffusion Coefficient	5.9 µm²/s	**Intercept g1²**	0.6997
Transmittance	82.8 %	**Baseline**	1.187

Fig. 14: Graph of particle size of NE10 formulation



Results

Hydrodynamic diameter	68.05 nm	**Mean intensity**	345.4 kcounts/s
Polydispersity index	23.6 %	**Absolute intensity**	1439.3 kcounts/s
Diffusion Coefficient	7.2 µm²/s	**Intercept g1²**	0.7433
Transmittance	75.7 %	**Baseline**	1.081

Fig. 15: Graph of particle size of NE22 formulation

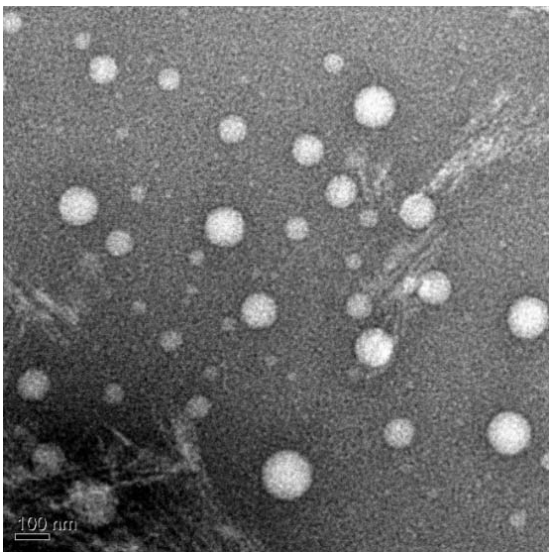


Fig. 16: Transmission electron microscopy (TEM) Images of optimized SNEDDS

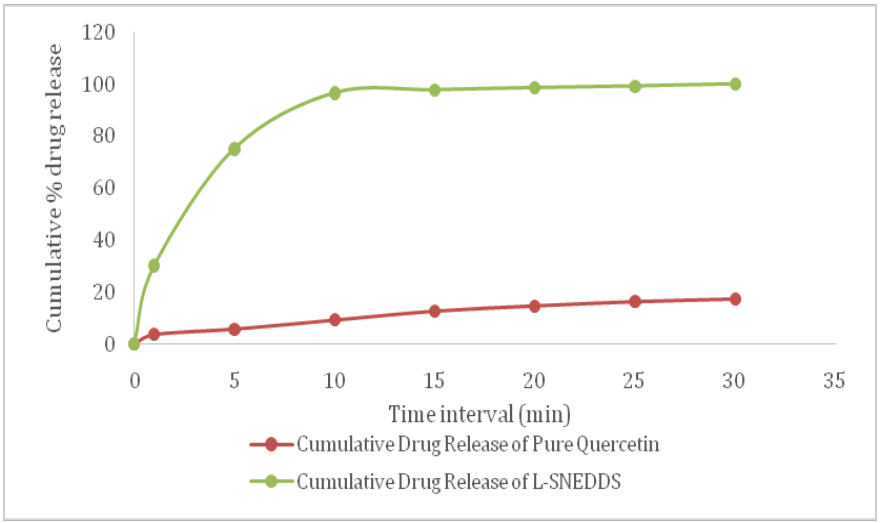


Fig. 17: *In vitro* drug release of NE4 and pure drug in 0.1N HCl (n=3)

Table 7: Particle size of the liquid SNEDDS containing quercetin

S. No.	Formulation code	Particle size (nm)	% PDI
1.	NE4	11.96 nm	22.1%
2.	NE10	83.06 nm	23.5%
3.	NE22	68.05 nm	23.6%

From the table 7, it was found that NE4 formulation has a smaller particle size and PDI as compared to the other two formulations. In case of NE4, the particle size was found to be 11.96 nm and the percentage polydispersity index was 22.1%.

***In vitro* drug release study**

The in vitro release of the drug from the optimized SNEDDS of Quercetin (NE4) revealed a significant increase drug release rate of formulation than the pure drug. The data of drug release of 30 min have shown maximum drug release (99.70±0.227%) of Quercetin from its SNEDDS. Furthermore, the release profile of Quercetin from its SNEDDS also showed that it yielded an immediate release profile.

CONCLUSION

Quercetin is a very promising bioflavonoid with mainly potential antioxidant activity. Despite its wide spectrum of pharmacological properties, the use of Quercetin in the pharmaceutical field is limited due to its poorly aqueous solubility and instability in physiological medium affecting its bioavailability. In this study self-emulsifying technology was used to formulate Quercetin into a stable dosage form with improved bioavailability.

Several oils, surfactants and cosurfactants were screened, from which Triacetin, Tween 20 and ethanol were selected respectively based on solubility and transmittance studies for the development of SNEDDS of Quercetin. The solubility of quercetin was found to be as high as 33.41±0.45 mg/ml in these formulations. Pseudo ternary phase diagram were constructed to determine the region of nanoemulsion formation and further SNEDDS were prepared which exhibited an acceptable pH of 6.5±0.15 and drug content of 95-100 %. Formulations were optimized using self-emulsification ability and robustness to dilution and the optimized formulation was further evaluated for stability and *in-vitro* dissolution. The optimized formulation showed high thermodynamic stability, acceptable particle size (≤200 nm), low viscosity and improved dissolution behavior. Drug release of 30 min have shown maximum drug release (99.70±0.227%) of Quercetin which is an *in vitro* indication of enhanced bioavailability. Results obtained to substantiate the development of a stable SNEDDS of Quercetin with enhanced bioavailability.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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