INTERNATIONAL JOURNAL OF PHARMA PROFESSIONAL'S RESEARCH

Development of SMEDDS for Enhanced Delivery of Quercetin: Addressing Challenges in Ocular Inflammation Management

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ABSTRACT

Innovative drug delivery methods are required for effective treatment of ocular inflammation, which continues to be a major challenge in ophthalmic therapeutics. Despite its low aqueous solubility and bioavailability, quercetin a naturally occurring flavonoid with strong anti-inflammatory properties has potential for managing ocular inflammation. In this study, the effectiveness of quercetin delivered via a novel ocular self-micro emulsifying drug delivery system (SMEDDS) was assessed. A UV-visible spectrophotometer was used in this experiment to determine the absorbance maxima (λmax) of quercetin. At pH 7.4, a phosphate buffer was used to create a calibration curve. An analysis was conducted using FT-IR spectroscopy to determine quercetin's compatibility with excipients. A formulation of Quercetin SMEDDS was created and assessed. The entrapment efficiency (%) was found to be 99.85%, viscosity 332.7cp, zeta potential -27.38 mV, droplet size 12.37 nm, invitro-drug release 89.55% in pH 7.4 Phosphate buffer solution. Results obtained from release kinetic study revealed that the drug release mechanism was found to be first order followed by Korsmeyer peppas kinetics. While stability study it was observed that, there were no appreciable changes in the formulation, and hence it was concluded that the formulation was thermodynamically stable. SMEDDS for quercetin exhibit good in vitro performance and encouraging formulation optimization, indicating potential for improved ocular delivery and the treatment of inflammatory conditions.

Keywords: *SMEDDS, Quercetin, Ocular Inflammation, Anti-Inflammation, Drug Delivery, Disease, Treatment*

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Volume 15, Issue 3, 2024, Received: 15 May 2024, **Accepted:** 16 July 2024, **Published:** 30 July 2024,
DOI: 10.69580/IJPPR.15.3.2024.105-126

1. Introduction

Self-microemulsifying drug delivery systems (SMEDDS) address the widespread problem of poor aqueous solubility in many proposed drugs, marking a paradigm shift in pharmaceutical science. By utilizing surfactants, oils, and co-solvents, SMEDDS create microemulsions that enhance solubilization, absorption, and dissolution in the gastrointestinal tract, improving oral bioavailability and stabilizing labile molecules. This process also adjusts release kinetics and bypasses absorption barriers, leading to more accurate and effective medication administration. SMEDDS offer flexibility and adaptability, integrating into various dosage forms, improving patient compliance, and supporting individualized treatment regimens. They are available in liquid and solid formulations, including capsules and tablets, and are easy to manufacture and scale up. Their stability in the gastrointestinal environment ensures steady efficacy, making them essential tools for overcoming the challenges posed by poorly soluble medications and advancing treatment approaches.[1-4]

SMEDDS have great potential for treating ocular disorders by overcoming limitations of traditional delivery methods. They can optimize treatment outcomes by improving drug solubility, extending retention time, and enhancing penetration into ocular tissues. SMEDDS have been studied for various eye diseases, including dry eye syndrome, glaucoma, uveitis, and age-related macular degeneration, where they can deliver personalized therapy approaches. The versatility of SMEDDS allows for different formulations, such as eye drops, ointments, or inserts, catering to patient preferences. Overall, SMEDDS show significant promise as advanced drug delivery systems for ocular therapies, offering the opportunity to enhance drug efficacy and improve treatment results.[5-7]

Ocular inflammation, or uveitis, involves the middle eye layer and can affect one or both eyes, causing symptoms like pain, redness, visual impairment, and floaters. If left untreated, it may lead to complications such as glaucoma and vision loss. Uveitis is categorized based on the affected uveal region and can be caused by infections, autoimmune disorders, trauma, or unknown factors. Treatment aims to reduce inflammation, relieve symptoms, and prevent tissue damage, primarily using corticosteroids, immunosuppressants, antimicrobials, NSAIDs, and cycloplegic drops, with

surgical interventions reserved for severe cases. A combination of these tailored treatments is often necessary to effectively manage ocular inflammation and preserve vision.[8-9]

Quercetin, a flavonoid found in various fruits, vegetables, and herbs, has gained attention for its potential therapeutic applications in ocular inflammation due to its diverse pharmacological properties, including antioxidant, anti-inflammatory, anti-allergic, and neuroprotective effects. The compound's anti-inflammatory mechanisms involve inhibiting the release of pro-inflammatory cytokines, scavenging free radicals to reduce oxidative stress, suppressing mast cell activation and histamine release, modulating immune responses, protecting retinal cells from injury, reducing vascular permeability, and potentially exhibiting synergistic effects with other compounds like resveratrol or omega-3 fatty acids. While preclinical studies and in vitro experiments have demonstrated the efficacy of quercetin in various models of ocular inflammation, further clinical research is warranted to evaluate its safety and efficacy in human subjects, explore optimal delivery routes and formulations, and unlock the full therapeutic potential of this promising compound for the management of ocular inflammatory conditions.[10-12]

2. Materials and Method

2.1 Materials

Different materials and equipment i.e., drug samples, oil, surfactant, co-surfactant, excipients and equipment, were obtained from different reputed companies.

2.2 Method

2.2.1 Determination of absorbance maxima (λmax) of Quercetin

The absorbance maxima (λmax) of Quercetin was determined utilizing a UV visible spectrophotometer (Shimadzu UV-1800 spectrophotometer). Quercetin 10µg/ml solution was determined between 200 to 400 nm.

2.2.2 Fourier transforms infrared (FT-IR) spectroscopy

Pharmaceutical substances are frequently identified using infrared spectroscopy as a technique. When the polymer-drug complex spectrum is compared to the separate spectra of the polymer and drug, FT-IR spectroscopy assists in verifying the complex's formation. FT-IR analysis was used to assess the drug's compatibility with the selected excipients. Using KBr pellet, FT-IR was used to assess the medication both by itself and in combination with specific excipients.[13]

2.2.3 Solubility studies

Quercetin (QT) solubility was assessed using a variety of oils (e.g., Transcutol P, Soybean oil, Ethyl oleate, Medium chain triglycerides), surfactants (e.g., Tween-80, EL-35), and co-surfactants (PEG 400 and propylene glycol). Excess QT was introduced to various oils, co-surfactants, and surfactants to assess the solubility. Next, the mixture was stirred for a maximum of 48 hours. After the samples were properly diluted with phosphate buffer pH 7.4, they were centrifuged for 10

minutes at 8000 rpm. After that, the drug was tested in supernatant using a UV spectrophotometer at 266 nm.[14]

2.2.4 Emulsification study

It was determined which surfactants could self-emulsify to select the best surfactant and cosurfactant. To account for the SMEDDS system's self-emulsification, transmittance and droplet size were measured. According to the specifications for the type IIIb spontaneous self-microemulsifying system, which produces incredibly tiny dispersions and induces the creation of small oil droplets more quickly than other systems, the oil content in the SMEDDS formulation was set between 10% and 15% (84–85). Various cosurfactants and surfactants were mixed (surfactant:cosurfactant ratio:1:1 [v/v]) and vortexed to produce homogenous mixtures. Once the oil phase was added, the mixtures underwent a gentle vortex. The self-emulsification efficiency was evaluated in the presence or absence of a selected drug based on transmittance and droplet size, and it was graded as excellent (grade A), good (grade B), fair (grade C), and poor (grade D).[15-16]

2.2.5 Construction of pseudo ternary phase diagram

The borders of the microemulsion domains were determined using the pseudo-ternary phase diagram. Phase diagrams were created to determine the proper concentrations of surfactant, oil, and co-surfactant. Based on the results of the emulsification and solubility tests, a ternary phase diagram was made using Tween-80 as the surfactant, Transcutol P as the oil, and Propylene glycol as the co-surfactant. Each component was the triangle's apex. Different ratios of co-surfactant, oil, and surfactant were used to construct a set of blank SMEDDS formulations for each of the three components. In any mixture, the total concentrations of the three components always add up to 100%. The microemulsion formation efficiency was measured by adding 10 µL of each mixture to 10 mL of distilled water and gently stirring the mixture with a magnetic stirrer. The microemulsion's apparent spontaneity was objectively confirmed by measuring the mixture droplet size using photon correlation spectrometry. The Smix ratio that showed the largest microemulsion area was selected for further investigation.[17-18]

2.2.6 SMEDDS formulation preparation

A blank SMEDDS formulation was made by mixing oil, surfactant, and cosurfactant. After that, the mixture was vortexed to produce a transparent, homogenous solution. 10.0 mg of QT was added to 100 µL of blank SMEDDS formulation to develop the QT-loaded SMEDDS formulation. Table 1 summarizes the formulation design of QT SMEDDS.

Table 1: Formulation design of Quercetin (QT) SMEDDS

S. No.	Transcutol P (% v/v)	Tween 80 (% v/v)	Propylene glycol (%v/v)
F1	5	25	70
F2	5.45	48.97	45.58

F3	8.88	52.25	38.87
F4	21	19	60
F5	14.11	27.16	58.73
F6	13.77	34.77	51.46
F7	11.20	37.23	51.57
F8	15.23	48.62	36.15
F9	20	35.13	44.86
F10	12.35	22.68	64.97

3. Evaluation of Quercetin (QT) SMEDDS

3.1 Droplet Size

A photon correlation spectrometer was used to measure the prepared SMEDDS droplet size of QT (Zetasizer Nano ZS; Malvern Instruments, Malvern, UK).

3.2 Rheological study

SMEDDS viscosity was measured with a Brookfield viscometer at 37°C (Brookfield DV-E viscometer). Spindle No. 40 was used and rpm was set at 12.

3.3 Drug content

In a volumetric flask, 100 mg of SMEDDS were dissolved in 100 ml of glacial acetic acid. Following filtering, 1 ml of the solution was pipetted out, transferred to a 100 ml volumetric flask, and diluted with glacial acetic acid to the appropriate level. The produced solution was analyzed spectrophotometrically at 266 nm. The QT concentration in SMEDDS was established using the medication's standard calibration curve.

3.4 Zeta potential

Double-distilled water (DDW) was used to dilute the drug-containing SMEDDS formulation (20 µL) that was optimized. The SMEDDS were carefully shaken and then put into an optical polystyrene cuvette to calculate the zeta potential.

3.5 *In-vitro* release studies

An in-vitro release test was conducted using the USP XXIV method, and 500 mL of freshly made pH 7.4 phosphate buffer was used as the dissolution medium. The gadget had a 100 rpm setting and was maintained at 37°C. The dissolving process was carried out using a dialysis bag. (USA: Sigma Aldrich; MWCO 12,000 g/mole). Before each release experiment began, the dialysis bag was prepared by immersing it in dissolution medium for an entire 24-hour period. SMEDDS loaded with quercetin were firmly secured with a thermoresistant thread in a dialysis bag holding 5 mL of dissolving medium. At regular intervals, 1 mL sample was taken (10, 20, 30, 40, 60, 120, 180, 240, 300 and 360 min.) and dissolution medium aliquot amount was replaced to maintain sink

condition. The drug content of the samples was ascertained by using a UV visible spectrophotometric method set at 266 nm.[19]

3.6 Selection of best batch of QT-SMEDDS

Based on the evaluation of prepared SMEDDS formulations, one best batch was selected which was further evaluated for TEM, release kinetic study and thermal stability study.

3.7 Transmission electron microscopy

A Transmission Electron Microscope (JEM 1010, JEOL Ltd, Tokyo, Japan) was used to analyze the morphology of emulsion droplets in order to improve the formulation of QT-loaded SMEDDS, using an acceleration voltage of 80 kV. An optimal SMEDDS formulation was created and diluted with water 1:1,000. One drop of the sample was put directly onto copper mesh, and it was dried at 25°C.

3.8 Release kinetic study

The data of in-vitro dissolution study was fitted into different kinetic models to check out drug release mechanism from prepared self-microemulsifying system.[20]

3.9 Thermodynamic stability studies

Because medication precipitating in an excipient matrix might adversely affect a formulation, physical stability is critical to its efficacy. The bioavailability and therapeutic effectiveness of a formulation may be impacted by phase separation of the excipients as a result of insufficient physical stability. Furthermore, partial release, delayed drug breakdown, softness, and brittleness may arise from formulation incompatibilities with the gelatin shell of the capsules. The following cycles are carried out for these studies:

3.9.1 Heating cooling cycle

6 heating and cooling cycles, ranging from 4°C in the refrigerator to 45°C at high temperatures, were carried out, each lasting at least 48 hours. Afterward, those formulations underwent the centrifugation test, which demonstrated their stability.

3.9.2 Centrifugation

Formulations that successfully complete the heating-cooling cycle are centrifuged for 30 minutes at 3500 rpm. Formulations that do not show phase separation were chosen for the freeze-thaw stress test.

3.9.3 Freeze-thaw stress cycle

3 freeze-thaw cycles are carried out between 21°C and 25°C, each lasting at least 48 hours. A formulation is said to have high stability if it passes this test and exhibits no signs of phase

separation, creaming, or cracking. The formulations are then put through a dispersibility test to see how effectively they self-emulsify after this test.[19]

4. Results and Discussion

4.1 Experimental work

4.1.1 Determination of absorption maxima of quercetin

The λmax of (10µg/ml) solution of Quercetin in pH 7.4 phosphate buffer was found to be 266 nm as shown in figure 1.

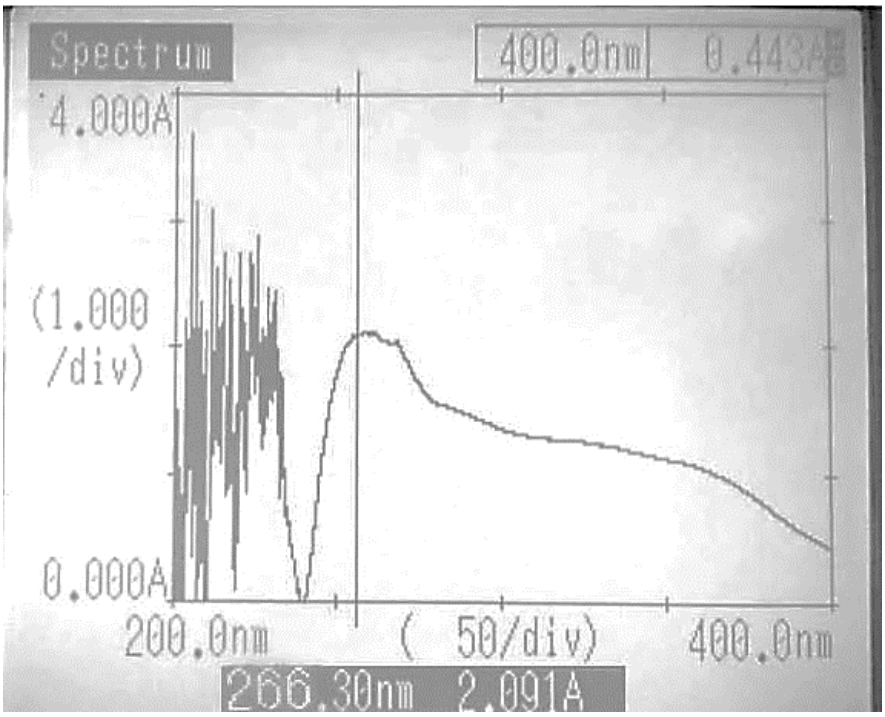

Figure 1: λmax of Quercetin in phosphate buffer pH 7.4

4.1.2 Preparations of Standard calibration curve of Quercetin in phosphate buffer pH 7.4

The serial dilutions of Quercetin in concentration range of 10-50 µg/ml were prepared and absorbance was taken on U.V. visible spectrophotometer at 266 nm. Standard calibration curve of Quercetin was constructed in between concentration and absorbance as shown in table 2 and figure 2. It was found that Quercetin showed good linearity (y=0.0023x-0.0002, R^2=0.9996).

Table 2: Standard Calibration curve of Quercetin in Phosphate buffer pH 7.4

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.00
2	10	0.024
3	20	0.046

4	30	0.069
5	40	0.093
6	50	0.118

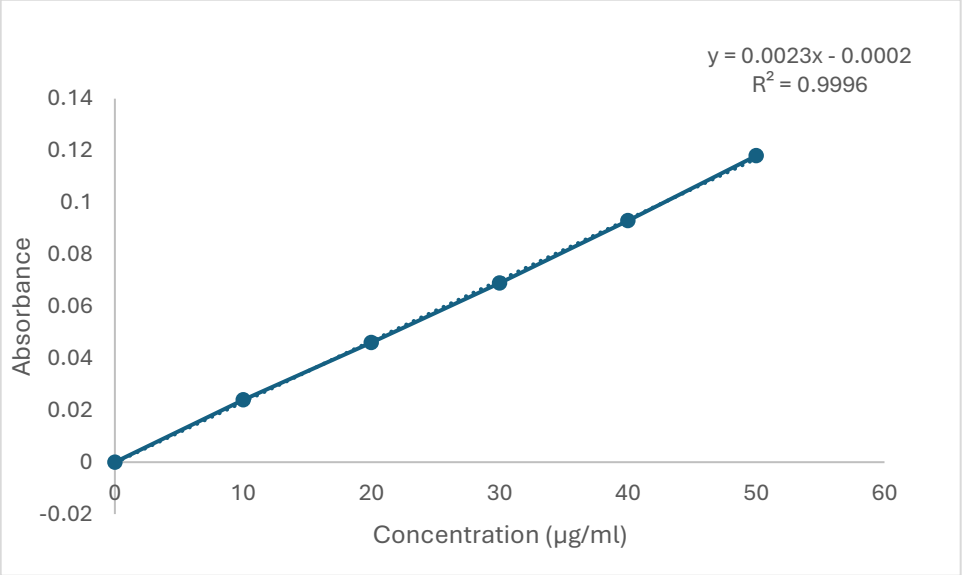

Figure 2: Standard calibration curve of Quercetin in pH 7.4 Phosphate buffer

4.1.3 FTIR spectroscopy

The drug alone and in combination with selected excipients was analyzed by FT-IR using KBr pellet. FTIR spectra of Quercetin (pure drug) and formulation blend were presented in figure 3 & 4. It was observed that peaks of Quercetin were retained in FTIR spectra obtained with Quercetin and other selected excipients.

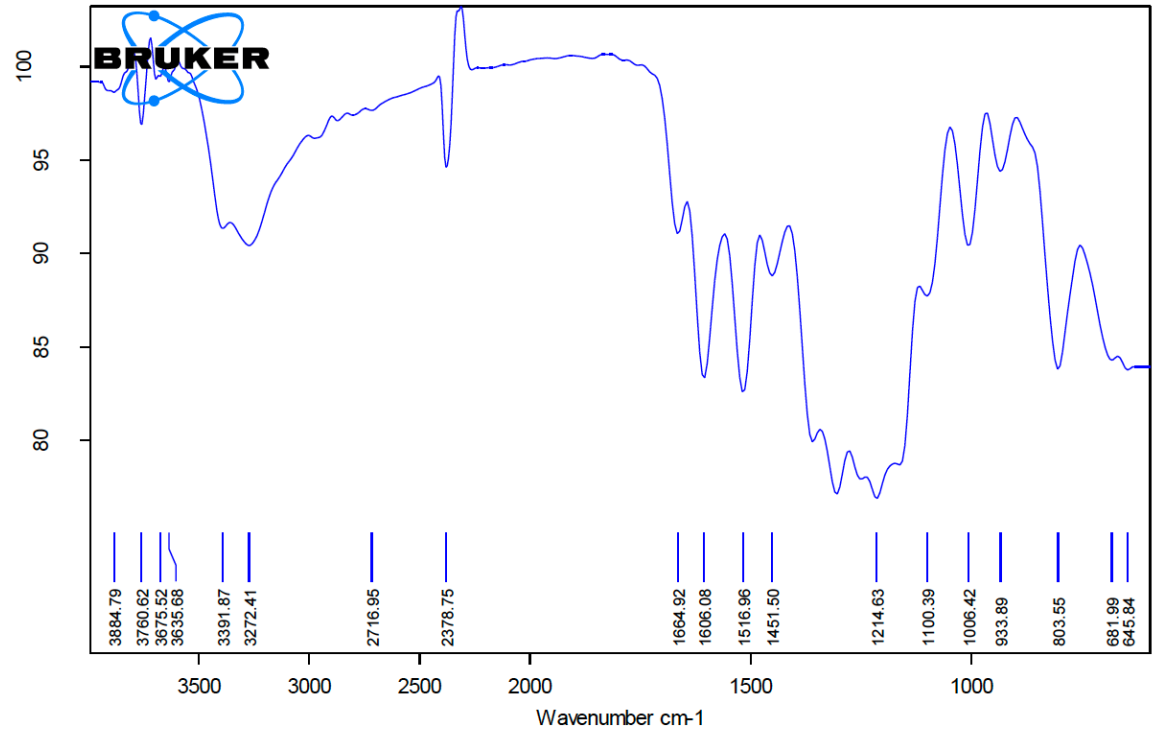

Figure 3: FTIR spectra of Quercetin (Pure drug)

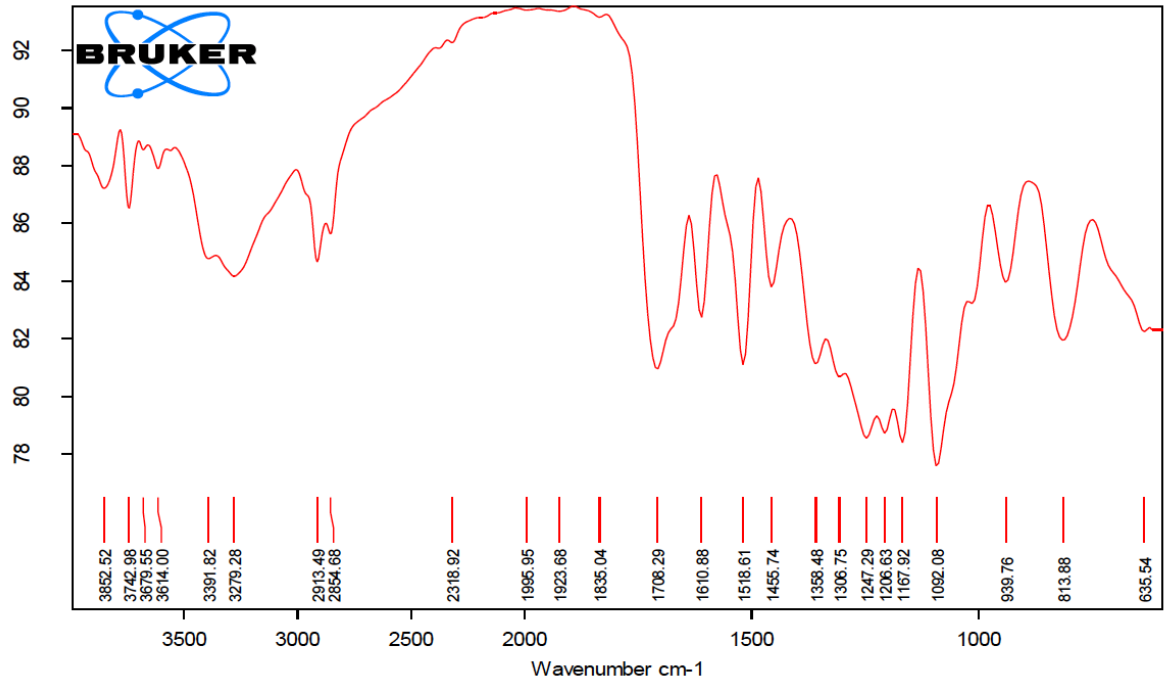

Figure 4: FTIR spectra of Formulation blend

4.1.4 Solubility of Quercetin (QT) in selected excipients

Components exhibiting high Quercetin solubility should be chosen because the active ingredients solubilization in a SMEDDS formulation is crucial for creating dispersion systems. Table 3 and Figure 5 show quercetin solubility in various excipients. It was observed that Transcutol P showed significantly higher solubility for Quercetin (282.89±0.45mg/mL) than other oils (3.26±0.12–45.72±0.38 mg/mL). Because oils have a tendency to solubilize hydrophobic drugs, quercetin's solubility in the SMEDDS oil component is significant. Transcutol P was therefore chosen as oil phase for creating the SMEDDS. Among the surfactants screened, Tween 80 has better solubility (39.21±0.18mg/ml) for Quercetin. Among the cosurfactants screened, Propylene glycol showed better solubility (0.83±0.11mg/ml) for Quercetin than PEG400 (0.561±0.12). The chosen cosurfactant and surfactant quickly combine to form oil/water droplets. The emulsification efficiency of the chosen surfactant and cosurfactant served as additional confirmation.

Table 3: Solubility studies of quercetin in different solvents

S. No.	Solvent	Solubility (mg/ml)
1.	**Transcutol P**	282.89±0.45
2.	**PEG 400**	0.561±0.12
3.	**Propylene glycol**	0.83±0.11
4.	**Tween 80**	39.21±0.18
5.	**EL-35**	0.119±0.19
6.	**Soybean oil**	45.72±0.38
7.	**Medium chain triglycerides**	3.26±0.12
8.	**Ethyl oleate**	22.71±0.22
9.	**Water**	0.117±0.11

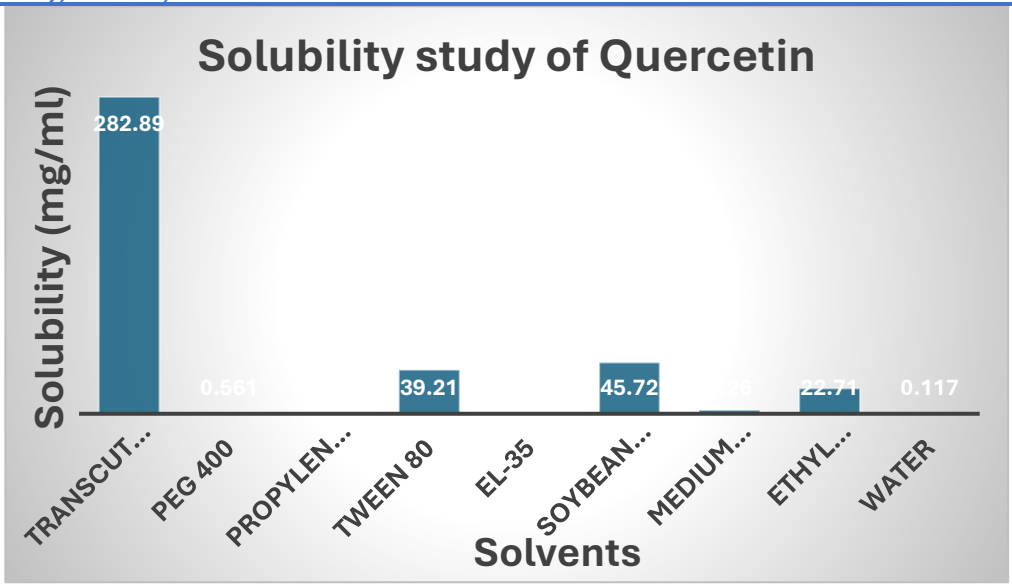

Figure 5: Quercetin Solubility Determination in the Various Oils, Surfactants and Co-surfactants

4.1.5 Emulsification Study

Grading standards were implemented in order to ascertain the capacity for self-emulsification, as indicated in Table 4. Using transmittance and droplet size, the surfactant's self-emulsification was assessed for dispersibility and final appearance. While self-emulsifying drug delivery systems typically produce emulsions with diameters ranging from 100 to 300 nm, the formulations of SMEDDS produce clear microemulsions with particles smaller than 100 nm. Large droplet size and subsequently poor microemulsification are indicated by a transmittance value between 50% and 80%, whereas good microemulsification is indicated by a value over 80%. Compared to EL-35, Tween 80 showed a greater capacity to emulsify the selected oil. This might be because the surfactant's hydrophilic-lipophilic balance, chain length and structure, and the chemical structure of the oil under study all affect how well it emulsifies. Since they dissolve oils rapidly and readily in the aqueous phase, surfactants with higher hydrophilic-lipophilic balance values are better at emulsifying oils due to their hydrophilicity, which results in finer oil/water emulsions.

Table 4: Evaluation Standard for Self-Emulsification Efficiency

Grade	Emulsification capacity	Size (nm)	Transmittance (%)	Appearance
A	Excellent	<100	>90	Clear and transparent
B	Good	100-300	80-90	Slightly less clear and bluish white
C	Fair	300-1000	50-80	Milky or greyish white

D	Poor	NA	<50	No homogeneity

In the cosurfactants scenario, propylene glycol (PG) outperformed PEG400 in terms of emulsification efficiency, especially when paired with Tween 80. In the blank SMEDDS formulation, the Tween 80/PG system showed small droplets and high transmittance (grade A). The remarkable self-emulsification efficiency (grade A) of the SMEDDS formulation, which included the Tween 80/PG combination, was unaffected by drug-loaded circumstances. An oil-surfactant combination in contact with water can be more effectively emulsified by cosurfactants with higher hydrophilicity. As a result, PG and Tween 80 were selected as the cosurfactants for further study.

4.1.6 Construction of Pseudo-ternary Phase Diagram

A pseudo-ternary phase diagram was made using Tween 80 (surfactant), Transcutol P (oil), and Propylene glycol (cosurfactant) in a drug-free environment in order to determine the correct ratio of constituents in the SMEDDS formulation. The SMEDDS regions (dark grey area) were created with a volume ratio of 10%–80% surfactant/cosurfactant and 5%–20% oil, as shown in Figure 6. This resulted in a transparent homogenous dispersion. The SMEDDS region with a bluish white or less clear appearance is represented by dark grey area. The highest self-emulsifying capacity was found in the SMEDDS region, which was chosen for additional research even though all of formulations demonstrated better self-emulsifying capacity within one minute. When the formulation's oil content exceeded 50%, unstable emulsions formed. The SMEDDS formulation was then improved to ensure the best possible quercetin loading. Trials that followed involved adding 10.0 mg of QT to 100 µL of a specific SMEDDS system. QT precipitated or aggregated in certain formulations with a lower ratio of surfactant to cosurfactant.

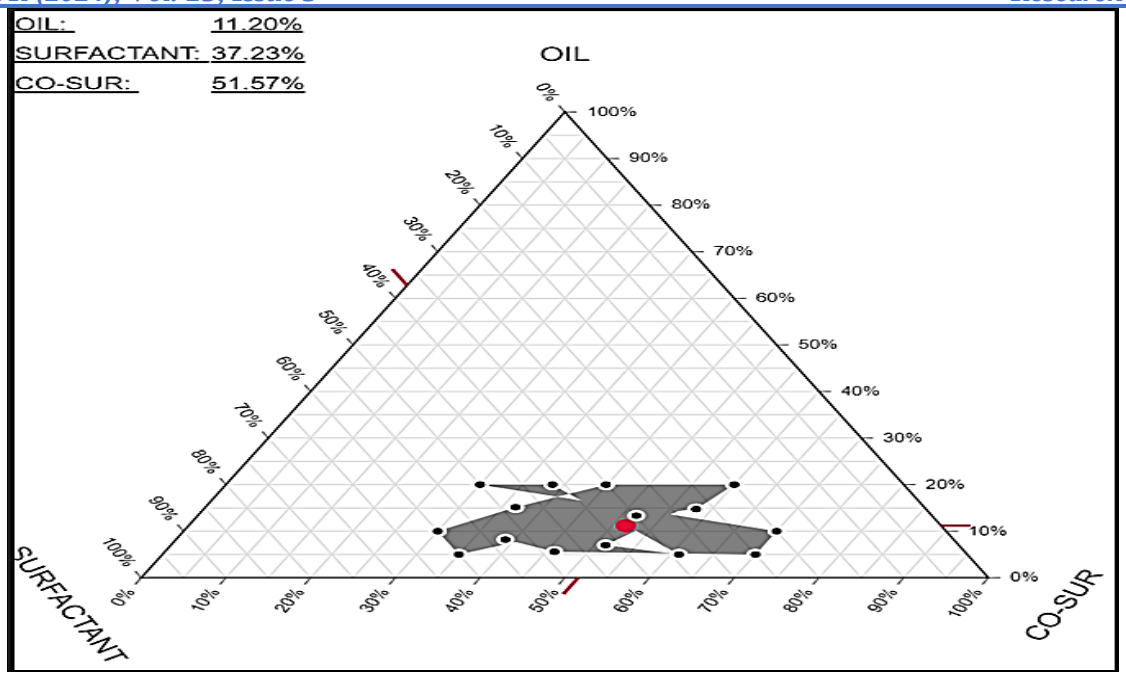

Figure 6: Pseudo ternary phase diagram of Quercetin (drug), Transcutol P (Oil), Tween 80 (Surfactant) and Propylene glycol (Co-surfactant)

4.1.7 Evaluation of Quercetin SMEDDS system

The prepared Quercetin SMEDDS system was evaluated for various evaluation parameters viz., droplet size, Rheological study, zeta potential, drug loading, and in-vitro dissolution study.

4.1.7.1 Droplet Size Determination

The SMEDDS batches droplet size (F1-F10) ranged between 12.37-55.61 nm. The following table represents the droplet size of prepared SMEDDS system (table 5 & Figure 7).

Table 5: Droplet Size of Quercetin SMEDDS batches F1-F10

S. No.	Formulation Code	Droplet Size (nm)
1.	F1	26.39
2.	F2	13.58
3.	F3	15.12
4.	F4	50.31
5.	F5	26.74
6.	F6	14.66

7.	F7	12.37
8.	F8	22.83
9.	F9	37.57
10.	F10	55.61

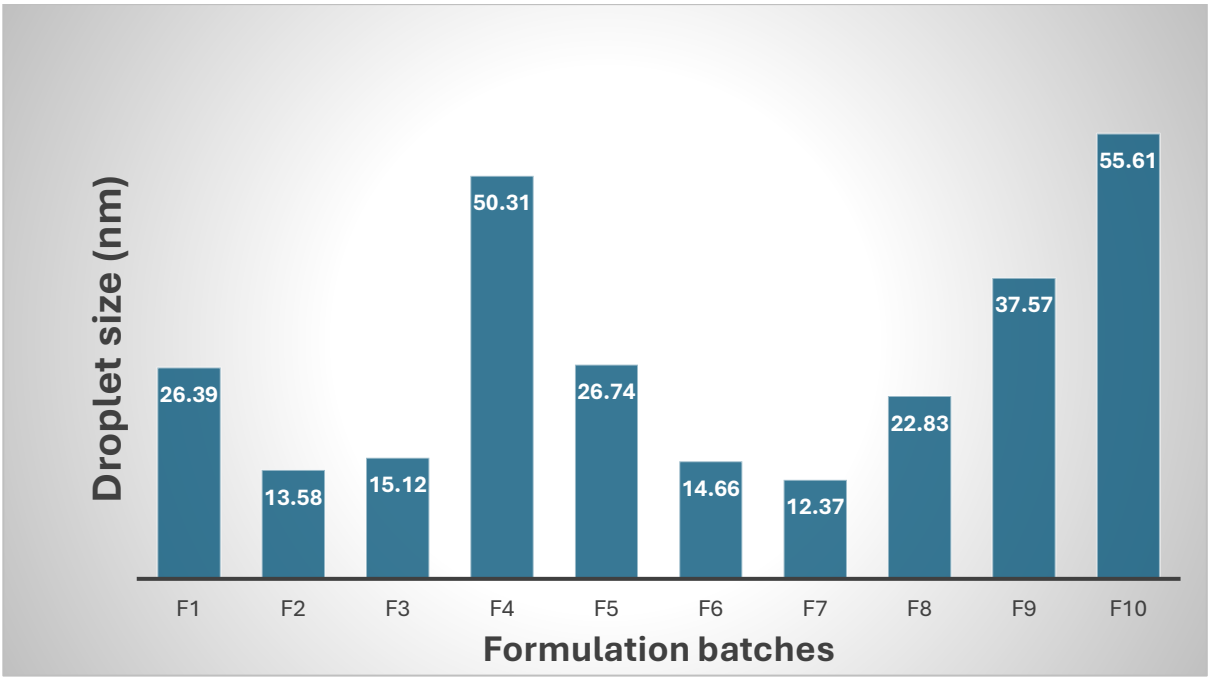

Figure 7: Droplet Size of Quercetin SMEDDS Formulation Batches (F1-F10)

The microemulsions in the current study had globule sizes ranging from 12.37 to 55.61 nm, which is regarded as an appropriate midrange that provided respectable homogeneity and a good size distribution.

4.1.7.2 Rheological Study

Viscosity of Quercetin SMEDDS formulation was determined by Brookfield's viscometer. The viscosity of SMEDDS formulation batches ranged between 332.7-662.8 cps (Table 6).

Table 6: The Rheological Studies of SMEDDS Formulation Batches (F1-F10)

S. No.	Formulation Code	Viscosity (cps)
1.	F1	455.2
2.	F2	516.3

3.	F3	422.6
4.	F4	643.7
5.	F5	582.6
6.	F6	548.4
8.	F7	332.7
9.	F8	497.4
10.	F9	662.8
11.	F10	432.5

4.1.7.3 Entrapment efficiency

Batch F7 demonstrated the highest entrapment efficiency of 99.85%, while batch F10 demonstrated the lowest entrapment efficiency of 91.78% (Table 7 & Figure 8).

Table 7: Entrapment efficiency of SMEDDS Batches (F1-F10)

S. No.	Formulation Code	% Entrapment efficiency
1.	F1	94.63
2.	F2	98.76
3.	F3	94.52
4.	F4	93.55
5.	F5	95.18
6.	F6	97.26
7.	F7	99.85
8.	F8	96.39
9.	F9	93.11
10.	F10	91.78

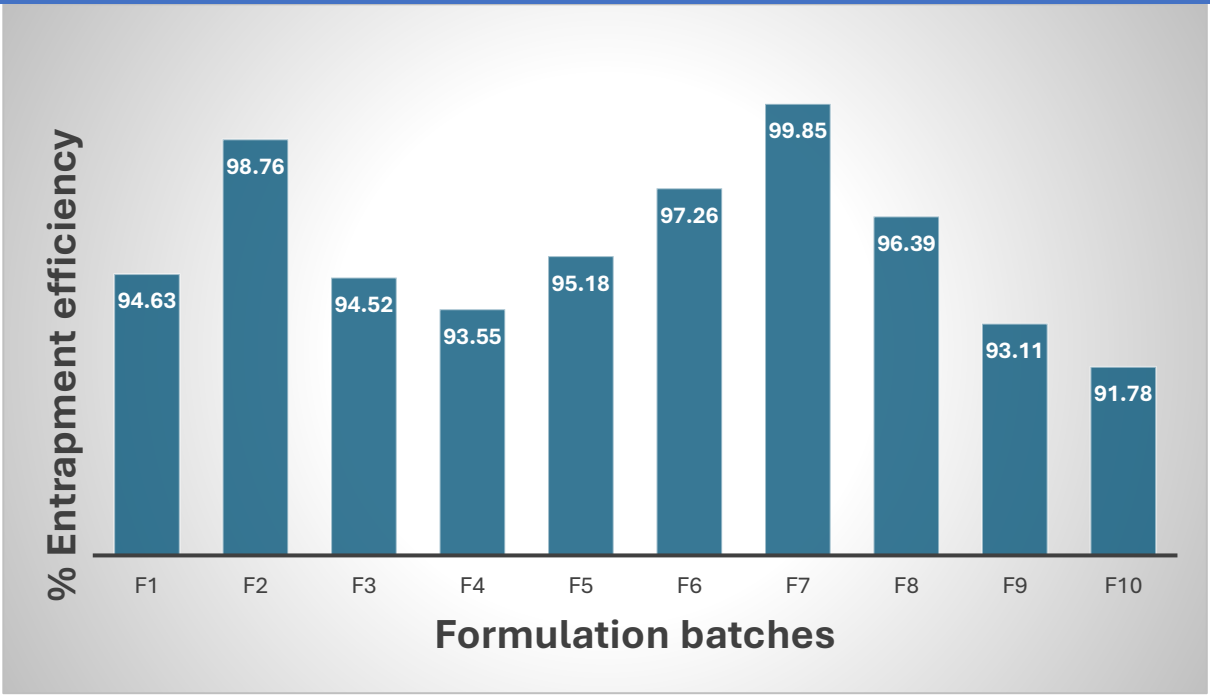

Figure 8: Entrapment efficiency of Quercetin SMEDDS Formulation Batches (F1-F10)

4.1.7.4 Zeta Potential Analysis

All ten batches were subjected to analysis using the Malvern zeta sizer. The outcomes are summarized in table 8.

Table 8: Zeta Potential Analysis of SMEDDS Formulation Batches (F1-F10)

S. No.	Formulation Code	Zeta potential mean (mV)
1.	F1	-30.27
2.	F2	-32.15
3.	F3	-35.45
4.	F4	-30.93
5.	F5	-31.56
6.	F6	-33.84
7.	F7	-27.38
8.	F8	-30.71
9.	F9	-33.27

10.	F10	-41.63
11	F11	-35.42

4.1.7.5 *In-vitro* release studies of Quercetin SMEDDS

An in-vitro drug release study of Quercetin-SMEDDS was conducted and data was presented in table 9 and figure 9. It was found that pertaining to micro emulsifying system, the maximum drug was released in first 15 min and then it was sustained further. The maximum drug release was obtained with F7 batch (89.55%) in 15 min.

Table 9: In-vitro drug release study of Quercetin SMEDDS

Time (min.)	% Drug release data of Formulation batches (F1-F9)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	43.56	47.82	47.19	44.37	43.78	46.51	48.65	45.27	44.18	45.62
10	64.79	68.45	67.61	65.51	64.25	67.31	67.93	66.54	64.27	65.14
15	86.18	89.33	89.01	86.74	85.51	87.59	89.55	86.79	84.58	86.75
20	85.43	88.55	88.76	86.28	85.32	87.13	88.94	86.34	84.21	85.98
30	85.15	88.12	88.28	85.95	84.56	86.86	88.85	86.11	83.86	85.56
60	84.43	87.85	87.41	85.43	84.33	86.65	88.42	85.26	83.52	84.64
80	83.61	86.62	87.23	85.13	84.12	86.22	87.85	85.01	83.23	83.91
100	82.38	86.25	86.85	84.85	83.94	85.89	87.18	84.92	82.91	83.37
120	81.76	86.14	85.97	84.43	83.56	85.49	86.71	84.33	82.47	83.08

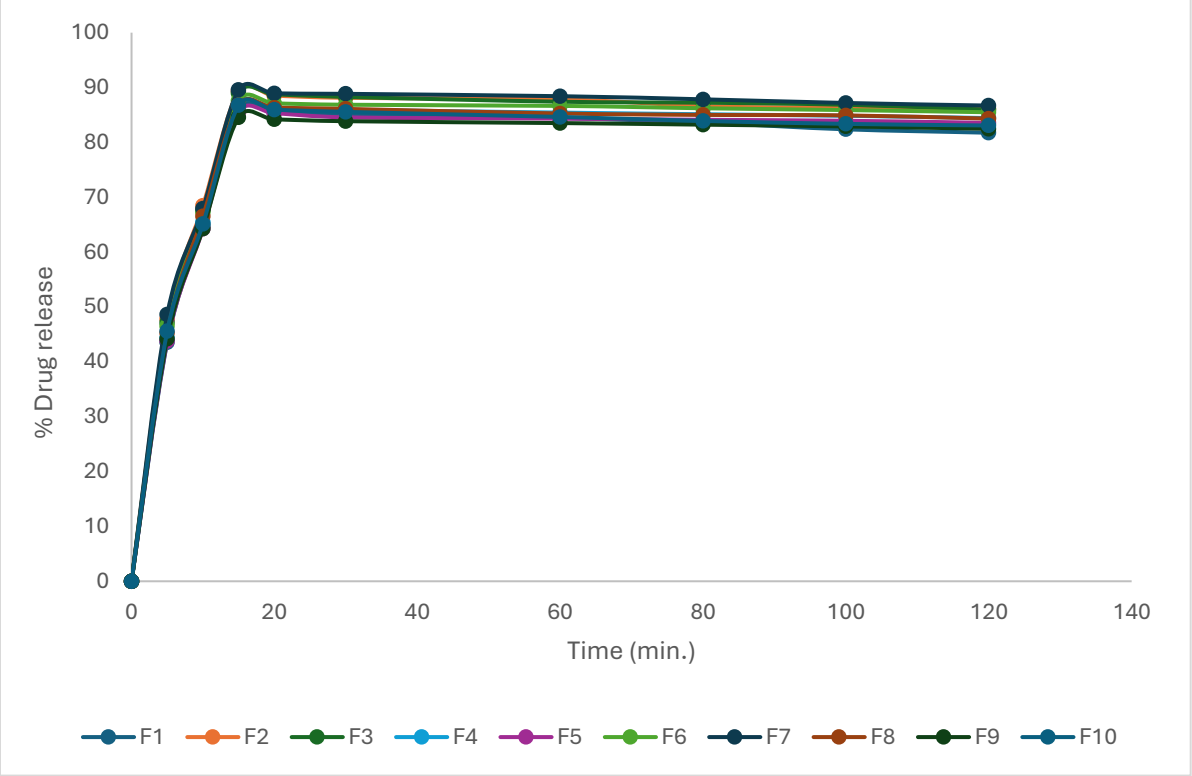

Figure 9: *In-vitro* drug release profile of Quercetin SMEDDS in pH 7.4 Phosphate buffer

Based on the evaluation parameters thus studied, it was found that batch F7 showed promising results in terms of droplet size (12.37 nm), viscosity (332.7 cps), % entrapment efficiency (99.85%), zeta potential (-27.38 mV) and *in-vitro* drug release (89.55%) and thus, considered as best batch (Table 10).

4.1.7.6 Evaluation Parameters for Best Batch of SMEDDS Formulation of QT

Table 10: Evaluation Parameters for Best Batch of QT-SMEDDS

S. No.	Parameter	Inference
1.	Entrapment efficiency (%)	99.85%
2.	Viscosity (cP)	332.7 cP
3.	Zeta potential	-27.38 mV
4.	Droplet size (nm)	12.37 nm
5.	*In- vitro* drug release	89.55% in pH7.4 PBS

This batch was further evaluated for Transmission electron microscopy (TEM), Release kinetic study and stability study.

4.1.7.7 Transmission Electron Microscopy

Transmission electron microscope was used to determine the emulsion droplet morphology for the optimized CBZ-loaded SMEDDS formulation. The result is depicted in figure 10.

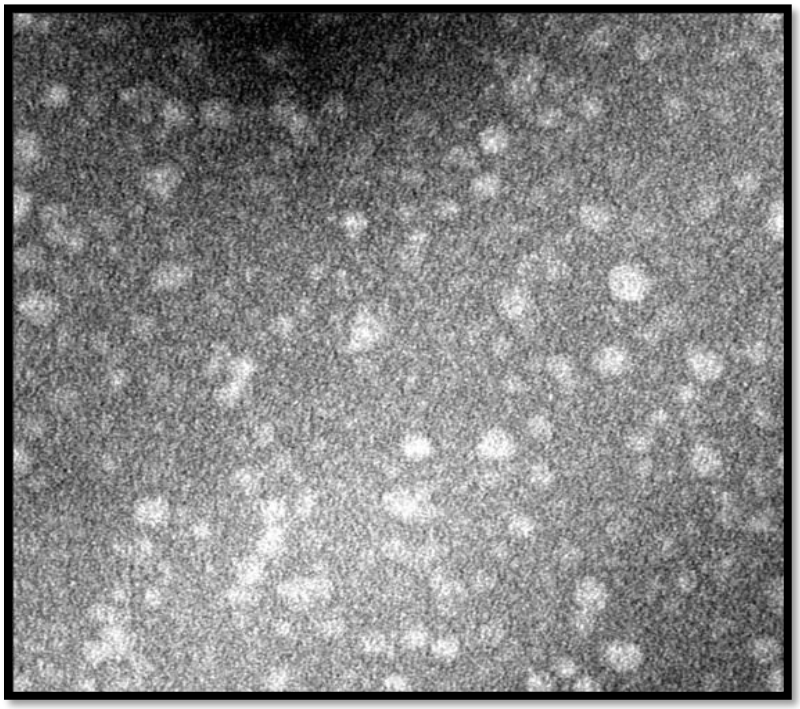

Figure 10: TEM Image of the Optimized QT-Loaded SMEDDS Formulation

4.1.7.8 Release Kinetic Study

To evaluate the mechanism of drug release from microemulsion in phosphate buffer saline (PBS) of pH 7.4, release data of best batch was fitted into a variety of kinetic models, including first & zero order, Korsemeyer-peppas & Higuchi models. Table 11 shows the data of release kinetics of drug.

Table 11: Estimated value of R^2 after fitting dissolution data of best batch of Quercetin SMEDDS formulation into various release kinetic models in pH 7.4 Phosphate buffer saline (PBS)

Formulation Code	Zero Order		First Order		Higuchi		Korsemeyer-Peppas	
	pH 7.4 Phosphate buffer saline							
	m	R^2	m	R^2	m	R^3	m	R^3

Quercetin SMEDDS	0.3932	0.625	0.0568	0.998	0.167	0.817	0.928	0.856

Results obtained from release kinetic study revealed that the drug release mechanism was found to be first order followed by Korsmeyer peppas kinetics.

4.1.7.9 Thermodynamic Stability Studies

Physical stability is important because the drug's precipitation in an excipient matrix can adversely affect the performance of the formulation. Phase separation of excipients due to inadequate physical stability of the formulation can impact both the therapeutic efficacy and bioavailability. For these investigations, the subsequent cycles were completed, and the outcomes are shown in Table 12.

Table 12: The observations of thermodynamic stability studies of all formulations

Formulation code	Heating cooling cycles	Centrifugation	Freeze thaw stress cycle
Quercetin SMEDDS	No Phase separation	No Phase separation	No Phase separation

From Table 12, it was found that, the formulation was determined to be thermodynamically stable because stability tests revealed no discernible changes to it. In the present work, the self-microemulsifying formulation (SMEDDS) of Quercetin was prepared and evaluated. Quercetin is a potential anti-inflammatory agent and can be utilized in the form of a suitable formulation for applications in ocular disorders. The present study showed promising results as per the desirability for ocular formulation, however, further, *in-vivo* study in a proper animal model is required to check out the potency of the prepared formulation in living organism, which would be helpful in formulating appropriate dosage for the society to get rid of ocular disorders and reducing the side effects of synthetic counterparts.

5. Conclusion

The utilization of SMEDDS for quercetin has shown substantial advancements in the optimization of formulation, characterization, and evaluation of performance. Through a systematic analysis of different oils, surfactants, and co-surfactants, we identified the optimal blends that improved quercetin's solubility and facilitated an extremely successful self-emulsification process. The findings indicate that SMEDDS is a promising method for delivering quercetin to the eyes. The formulation achieved 99.85% entrapment efficiency, 332.7 cp viscosity, -27.38 mV zeta potential, 12.37 nm droplet size, and 89.55% in-vitro drug release in pH 7.4 phosphate buffer, following first-order and Korsmeyer-Peppas kinetics. Stability tests confirmed the formulation's thermodynamic stability. This research highlights SMEDDS as a promising method for delivering

Quercetin to the eyes, with potential for future clinical validation in treating ocular inflammatory diseases.

6. Conflict of interest

The authors have no conflict of interest.

7. Acknowledgement

Authors are highly thankful to their Universities/Colleges for providing library facilities for the literature survey.

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