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"Formulation and Evaluation of Nano Emulsion to Enhance the Solubility of Rutin Trihydrate"

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KEYWORDS

Nano emulsion

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ABSTRACT:

Introduction: Rutin trihydrate is a chemical with low water solubility, and the purpose of this research is to improve its oral bioavailability by developing and characterizing a nanoemulsion formulation. Nano emulsions were created by ultrasonic emulsification with orange oilas the oil phase, Polysorbate 80 as the emulsifier, and Polyethylene Glycol 200 as the cosurfactant. To enhance the formulation, methods such as component screening, the development of pseudo-ternary phase charts and thermodynamic stability studies were used.With a tiny droplet size (58.0 ± 0.27 nm), high drug content (99.03 ± 2.14%), excellent transmittance (99.78 ± 0.03%), and good zeta potential (−22.9 mV), the optimized nanoemulsion demonstrated physical stability. A considerably greater release rate (79.67 ± 0.23% in 30 minutes) was found in in vitro drug release experiments than in the isolated drug (46.75 ± 0.35%). First-order kinetics that is non-Fickian diffusion mechanism were used to release the drug. According to these results, nanoemulsion technology holds promise for enhancing the oral administration of hydrophobic medications such as rutin trihydrate.

Objectives: This study aims to formulate and evaluate of Nano emulsion of rutin trihydrate to improve the solubility.

Methods: Dakshin (2015) claims that the ultrasonication method was used to manufacture nanoemulsions. Add orange oil and rutin trihydrate to a beaker and mix continuously. In a separate beaker, mix the cosurfactant and surfactant (Smix) together while stirring continuously. After that, The oil phase was constantly swirled at 300 rpm as Smix was added progressively. The oil and smix solution mixture was then gradually mixed with the aqueous phase while being constantly swirled at 600 rpm. After creating a nanoemulsion with an ultrasonic probe sonicator, the coarse emulsion was sent through a high-speed homogenizer set to 1700 rpm. Since the sample could be harmed by probe sonication,All of the pre-emulsion samples were maintained in a cold bath during the experiment to lessen the ultrasonic thermal effect of the probe sonicator. The nanoemulsion preparation schematic

Results: The formulated Rutin Trihydrate showed particle size in the desired range, drug content in the Nano emulsion which is consistent across batches, and in vitro drug release studies exhibited immediate drug release. Formulation batch N-6 concluded as our optimized batch, showed best desired properties including high percentage of drug content, % of Transmittance and Immediate drug Release, further nano emulsion were formulated of optimized batch which exhibited in-vitro drug diffusion.

Conclusions: It was concluded that it is possible to optimize the release of Rutin trihydrate for better therapeutic efficacy. Rutin trihydrate prepared using orange oil, PEG 200, Tween 80 was found to be suitable to for the Immediate release formulation and also Rutin trihydrate containing Nano emulsion showed the Immediate release action.

1. Introduction

appealing systems for use in the pharmaceutical business. In the pharmaceutical sector, nanoemulsions are used as Methods of delivering lipophilic bioactive compounds like specifics. One high- energy fashion for creating nanoemulsions is ultrasonic emulsification. This

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process is known to be quick and effective for creating stable nanoemulsions with low polydispersity and extremely small drop compasses (1). multitudinous molecules with bettered effectiveness and remedial eventuality have been developed as a result of advancements in drug discovery. still, because of their limited arid solubility, analogous intriguing remedial mixes constantly have poor oral bioavailability. This is a significant barricade to the pharmaceutical sedulity's sweats to manipulate these treatments. therefore, in order to satisfy the medicine's remedial window of effectiveness, the discovery of analogous drug molecules should be accompanied by the creation of novel and clever medication delivery systems that can deliver the treatments with advanced bioavailability. The absorption rate of medicine products in gastrointestinal fluids is primarily determined by the drugs' solubility and rate of dissolution(2). limited solubility GI lumen declination, limited membrane penetration, Andre- systemic concurrence can each contribute to low bioavailability. According to some estimates, up to 40 of the pharmaceutical sedulity's current discoveries of new chemical realities (NCEs) and multitudinous of its current specifics are lipophilic or deficiently answerable chemicals, which affect in low oral lack of capsule proportionality, bioavailability, and significant both inside and between- subject variability. Consequently, the rate at which these substances are absorbed is managed by dissolution from the gastrointestinal (GI) lumen. In the times to ahead, the capability to distribute deficiently answerable drugs will come more vital as innovator enterprises calculate more on NCEs to induce a larger share of the pharmaceutical request's profit.(Among the factors impacting oral bioavailability are arid permeability of drugs, solubility, dissolving rate, initial pass- systemic metabolism, and perceptivity to processes of efflux. The bioavailability of medications taken orally is being improved in a variety of methods. One useful system is to include the Liposomes and other inert lipid carriers contain an active lipophilic component. Because of their reduced poison and capability to greatly boost the specifics' bioavailability, nano emulsions feel to have attracted the topmost interest of all these strategies. an combination of translucent or clear oil that is isotropic oil driblets that are kinetically stable and distributed in an arid phase is stabilized with a drop size of less than 100 nm and an interfacial coating of molecules of surfactants and co-surfactants. they hold the utmost pledge for the oral administration of medications that are deficiently answerable in water because they meliorate coverage of the active component from enzymatic decline solubility.

2. Materials and methods

1) Materials

Rutin trihydrate is a Dham Tec Pharma product and a Navi Mumbai consultant. Tween 80 was bought from Sini Arcade Kasheli, taluka Bhiwandi-421302, PEG 200 was bought from LOBA CHEMIE PVT. LTD (Mumbai), and orange oil was bought from Mumbai 400 002 (India), Research-Lab Fine Chem Industries.

2) Methods

Preparation of Nano emulsion: Dakshin (2015) claims that the ultrasonication method was used to manufacture nanoemulsions. Add orange oil and rutin trihydrate to a beaker and mix continuously. In a separate beaker, mix the cosurfactant and surfactant (Smix) together while stirring continuously. After that, the oil phase was constantly swirled at 300 rpm as Smix was added progressively. The oil and smix solution mixture was then gradually mixed with the aqueous phase while being constantly swirled at 600 rpm. After creating a nanoemulsion with an ultrasonic probe sonicator, the coarse emulsion was sent through a high-speed homogenizer set to 1700 rpm. Since the sample could be harmed by probe sonication, All of the pre-emulsion samples were maintained in a cold bath during the experiment to lessen the ultrasonic thermal effect of the probe sonicator. The nanoemulsion preparation schematic.

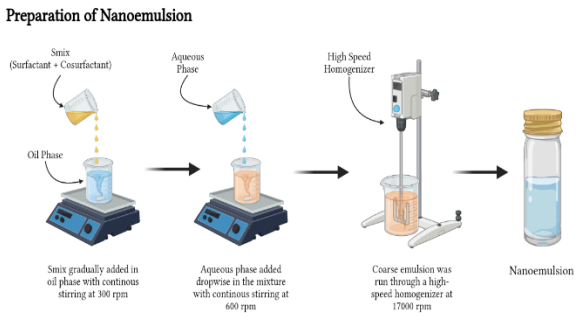

Figure1: Schematic diagram Representation of Nano-emulsion

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JCHR (2025) 15(5), 320-328 | ISSN:2251-6727

2.1) Component screening

The solubility of particular that are not properly answered in oil, surfactants, and cosurfactants is the most crucial criterion for evaluating components for nanoemulsion. Considering that this study's objective is to provide an oral expression, the solubility of the medication in oil is very significant because it has a significant impact on the nanoemulsion's ability to keep the medication in its solubilized form. To find out how soluble rutin trihydrate is in specific oil, surfactants, and cosurfactants, such as orange oil, castor oil, olive oil, sunflower oil, clove oil, Tween 20, Tween 40, Tween 80, PEG 200, propylene glycol, and PEG 400, one milliliter of each of these substances could be mixed with a redundant quantum of the medication. Following their removal from the shaker, the samples were centrifuged. 15 Minutes at 1500 rpm. They used a 0.45 mm membrane sludge to filter the supernatant. UV light at 257 nm was used to measure the amount of rutin trihydrate in oil, surfactants, and co-surfactants.

2.2] Preliminary ternary phase diagram analysis

Orange oil painting was chosen as the oil painting phase grounded on the medicine's solubility studies. Phase plates were also created using the waterless phase, cut 200 as a cosurfactant, and Tween 80 as a surfactant. For phase trials, a range of oil painting, surfactant, and cosurfactant fusions were used. For every group, surfactant along with cosurfactant (Smix) was mixed together at various weight ratios (1:1, 2:1, and 3:1). These rates of Smix were named for a thorough analysis of the phase plates for the creation of nano emulsion as the attention of surfactant relative to cosurfactant and cosurfactant relative to surfactant increased. oil painting and a certain Smix rate were completely mixed in each spectacle in weight rates ranging from 19 to 91 for each phase illustration. Seventeen distinct oil painting and Smix rates were developed in order to cover the maximum rates demanded allowed the study to clearly display the phase boundaries as they were defined in the phase plates 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, and 2:1. The pseudo-ternary phase plates were produced using the waterless titration system. Following a slow titration with an waterless phase on each weight rate for Smix and oil painting, transparent and readily flowable o/ w nanoemulsions were visually detected. A pseudo-three-component phase illustration was used to illustrate the nanoemulsion's physical condition. The waterless phase was represented by one axis, oil painting by another, and a admixture by the third of surfactant and cosurfactant at specific weight rates (Smix rate).

2.3] Choosing formulations from phase diagrams

Based on the following criteria, different formulations were selected from the Nano-emulsion area of each produced phase diagram to incorporate the medication into the phase of oil.

a) To fully dissolve a single dosage of the medication, the oil's concentration should be changed based on how soluble the medicine is in it. How much medication dissolves in one millilitre of oil

(b) to determine whether the medication has any effect on the phase diagram's or phase behaviour's nano-emulsion region.

(c) The Smix lowest concentration was found for that quantity of oil. Numerous formulas were tested for thermodynamic stability.

2.4] Research on thermodynamic stability

1. Heating-cooling cycle: Six cycles, each lasting at least 48 hours and varying from 4°C in the refrigerator to 45°C, were analyzed. For those formulations that held up well at these temperatures, centrifugation tests were conducted.

2. Centrifuge use: The formulations that received approval were subjected to centrifugation for 30 minutes at a speed of 3500 rpm. In the formulations used for the Test of freeze-thaw stress, phase separation was not apparent.

3. Freeze-thaw process : Each of the three Test of freeze-thaw stress, which went from -21°C to +25°C, involved storing the formulations for a minimum of 48 hours.

3) Characterization of Nano-emulsions

1)The transmittance percentage measurement of transmittance as a percentage. The % transmittance research was used to assess the clarity of the prepared Nanoemulsions. A UV-Vis spectrophotometer (Shimadzu 1800, Japan) was used for this investigation, with deionized water serving as the blank and the drug's Lambda max being 257 nm.

2) Size of Droplets
The selected samples were measured for particle size using a Zetasizer Nano ZS photon correlation spectroscopy (PCS) equipment (Horiba, UK). Double-

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JCHR (2025) 15(5), 320-328 | ISSN:2251-6727

distilled water was used to dilute the formulations (50 ml) to 2 ml. before to the measurements in order to avoid particle interactions and further scattering.

3) Infrared spectroscopy using the Fourier transform (FTIR)

Using a FTIR 8400 Shimadzu spectrophotometer, the produced nanoemulsion's Fourier transform infrared spectroscopy (FTIR) spectra were captured.13 The sample went into the sample holder. The drug's FTIR spectra were examined between 4000-1000 cm-1.

4) Zeta potential, which is the charge of a particle

The charge of the particles dictates the physical stability of the nanoemulsion. In an electrical field, the electrophoretic mobility of patches quantifies the zeta implicit value, which is a measure of particle charge. Using a Delsa Beckman Coulter Nano C flyspeck analyzer, USA, the zeta eventuality of the enhanced expression was determined (Tamilvanan and Benita 2004).

5) Viscosity

With spindle # CPE63 at 25 ± 0.5 °C and 100 rpm, the viscosity of the formulations was determined using a Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield Engineering Laboratories, Inc., Middleboro, MA). Rheocalc V2.6 was utilized for the computations.

6) Drug content

To find the drug concentration, one milliliter of the nanoemulsion formulation was dissolved in ten milliliters regarding methanol. For 30 minutes, this formulation was kept at 370.5°C and 50 rpm in a shaking incubator (Lab Tech Co., South Korea, LSI-2005 RL). The UV-1700 Pharma Spec from Shimadzu, a Japanese manufacturer, was utilized to analyze the supernatant at 210 nm after 30 minutes, with methanol acting as a blank (Shahnaz et al. 2011). (10)

7) In Vitro Drug Release Study

An investigation regarding the release of medications was carried out using a dissolving outfit type II (ElectrolabTDT-08L). The dissolving solution was nine hundred milliliters of disassembled stomach liquid having a pH of 1.2. Every Nano emulsion formulation was evaluated under various pH conditions while enclosed in a dialysis membrane bag. A 5 mL sample was taken and swapped out for a fresh medium at predetermined intervals. Before Every sample was examined with a calibrated UV-Vis spectrophotometer to 256 nm as the lambda maximum, it was filtered using a 0.45 mm hype sludge.

4) Results and discussion

Components screening by solubility determination

To choose the best oil phase, solubility tests were conducted. When compared to other oils, the results indicated that orange oil had the maximum solubility of rutin trihydrate (5.35 ± 0.56 mg/ml). According to the solubility test, ethanol and polyethylene glycol had the greatest ability to solubilize rutin trihydrate. According to the findings, the formulation's transparency can be significantly increased by using a combination of PEG 200 as a cosurfactant and Tween 80 as a surfactant.

Table 1. Analysis of oil's solubility

Sr. No	Components	Solubility(mg/ml)
	oils	
1	Orange oil	58.94±0.12
2	Castor oil	51.37±0.34
3	Clove oil	49.47 ±2.50
4	Sesame oil	33.98±0.24
5	Ethyle oleate	39.86±1.43
6	Isopropyl myristate	44.18±0.6
7	Sunflower oil	38.15±0.4

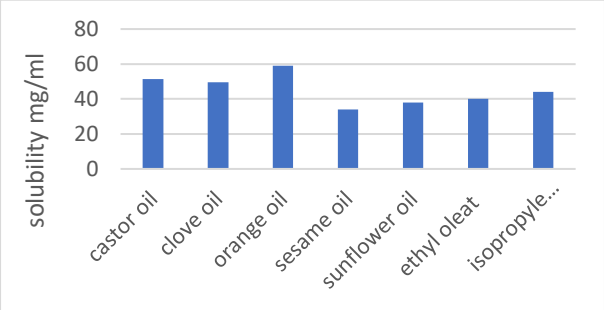

Figure 2: Data of oil solubility study of rutin trihydrate

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Table 2: Solubility study of surfactant and cosurfactant

Sr. No	Components	Solubility(mg/ml)
	Surfactant, cosurfactant	
1	Tween 80	58.33±0.4
2	Tween 20	21.35±0.22
3	Tween 40	40.25±0.13
4	PEG 200	52.37±0.65
5	Ethanol	37.95±0.03
6	PEG 400	45.38±0.24
7	Propylene glycol	40.52 ±0.50

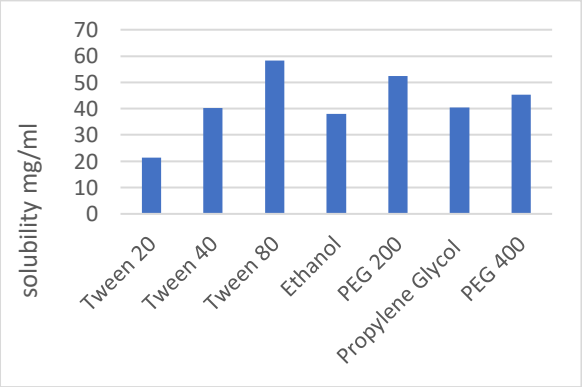

Figure 3: Data of surfactant, cosurfactant

Pseudo- ternary phase diagram construction

The elements that make up the pseudo-ternary phase plot are Smix surfactant/co-surfactant, oil painting, and deionized water. Due to its elemental flexibility, Smix can be found in surfactant/co-surfactant rates 1:1, 2:1, and 3:1. The darker part of the schematic of the pseudo-ternary phase indicates the area of nano-mixes, whereas the unshaded part indicates conflation zone. The Graphical plot for the pseudo-ternary phase for the coloured S blend rates of Tween 80 PEG 200 is shown in Figure (2). When the surfactant attention increased relative to the cosurfactant, the nano-conflation area decreased to the Smix rate 2:1 in Smix 3:1.

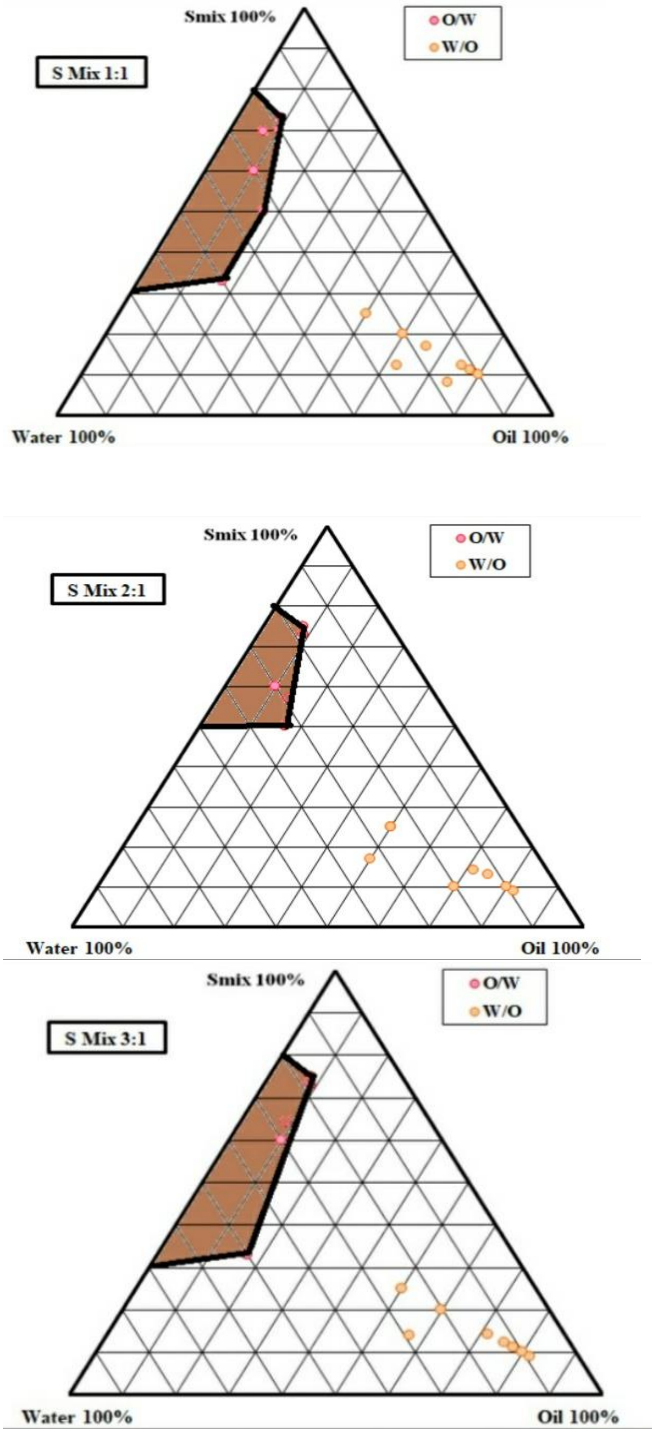

Figure 4: shows the O/W Nano-emulsion area at various Smix ratios using a system comprising various surfactant ratios (T80) to cosurfactant (PEG 200) shown by a pseudo-ternary diagram (1:1, 2:1, 3:1).

Journal of Chemical Health Risks
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JCHR (2025) 15(5), 320-328 | ISSN:2251-6727

Studies of thermodynamic stability

Heating and cooling cycles, freezing and thawing cycles, and centrifugation investigations were among the stability experiments performed on a few formulations from phase diagrams A, B, and C. Table 2 presents the findings. The formulations selected for size analysis were those that passed the stability tests.

Table 3 shows the results of thermodynamic stability tests for several formulations chosen from the diagram of phases.

Centrifugation; Freeze; H/C: cycle of heating and cooling. Tha: freeze-thaw cycle.

Physical Properties of Formulations for Nano emulsions (Mean ± SD n=3)

Table 4: pH Viscosity

Batch	pH	Viscosity
N-1	5.4± 0.09	70.5 ± 1.46
N-2	5.2± 0.52	56.3 ± 1.24
N-3	5.6± 0.26	72.2 ± 1.33
N-4	5.0± 0.08	61.9 ± 1.65
N-6	6.1± 0.26	78.3 ±1.47
N-7	5.4±0.24	62.8±1.45
N-8	6.5±0.04	55.74±1.65

Percentage of Transmittance

The improved nano-emulsion's transmittance % was 99.78±0.03.

Table 7: % of transmittance

Formulation Batch	% of Transmittance
NE-1	99.12 ±0.02
NE-2	99.01±0.04
NE-3	98.42±0.02
NE-4	99.43±0.05
NE-5	98.38±0.01
NE-6	99.78±0.03
NE-7	98.23±0.06
NE-8	98.56±0.07

Particle Size and Zeta Potential: The optimized batch of nano emulsion had a particle size of 58.0±0.27, a size distribution index (PDI) of 0.446, and a zeta potential of -22.9. Both of these parameters were determined to be N-6.

Table 5: Size of Particles and Zeta Potential, PDI

Formulation Batch	Particle Size	Polydispersity Index	Zeta potential (MV)
N-1	68.1±0.28	0.433	-45.1
N-2	132.6±0.30	0.272	-2.8
N-3	96.5±0.43	0.335	-13.8
N-4	125.3±0.54	0.242	-4.3
N-5	137.3±0.48	0.256	-7.8
N-6	58.0±0.27	0.446	-22.9
N-7	198.4±0.61	0.378	-19.1
N-8	203.8±0.64	0.347	-4.1

Drug content: The nano-emulsion optimized batch's drug content was 99.03±2.14%, indicating the nano-emulsion's good drug loading capacity

Table 8: Drug content

Formulation Batch	**Drug content %**
N-1	96.92±1.01
N-2	97.12±2.11
N-3	98.06±1.90
N-4	99.30±1.49
N-5	98.04±2.09
N-6	99.03±2.14
N-7	98.23±1.23
N-8	99.17±1.45

Study of drug release

Distilled water (pH 1.2) was used to test the drug release from the nano emulsion in vitro. The results showed that it had a maximal drug release of 79.67±0.23 within 30

Journal of Chemical Health Risks
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JCHR (2025) 15(5), 320-328 | ISSN:2251-6727

minutes because to its crystalline structure, lipophilicity, and low solubility. This is an example of a burst release during this time frame. The nano emulsion, on the other hand, accelerated the rate of breakdown and achieved a maximum drug release of 97.69±0.63 over 120 minutes. This might be because the droplets' modest size allowed for a vast surface area for the release of the medication. Consequently, it was shown that the nano emulsion formulation's release profile outperformed the commercial formulations by a significant margin (P > 0.001).

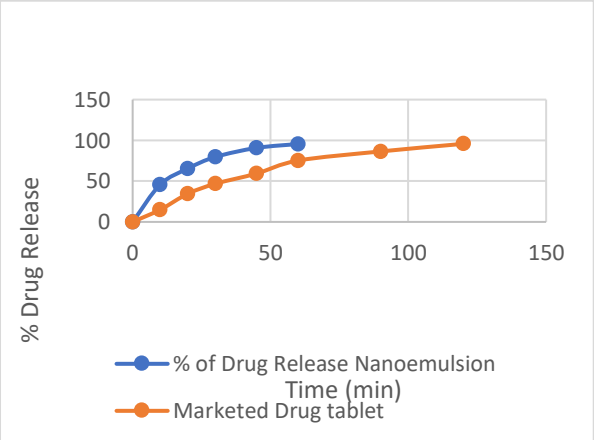

Figure 7: Drug release research in vitro

Investigation of the kinetics of drug release and the mechanism behind it

Four distinct kinetic Models are employed to characterize the release of the medication kinetics from the nano-emulsion. The drug release kinetics and medium from the nano-emulsion are estimated using these models. To find the model best suited for the release data, one must examine the correlation measure (r) values of all models. The model characterized by a high "r" value is the one that elegantly corresponds to the release data. Several kinetic models, such as zero order, first order, Korsmeyer-Peppas Model, and Higuchi angles, were necessary to fully comprehend the kinetics of the pharmacological release.

Figure 8 displays each of these models for the optimized expression. First order release kinetics (0.9792) were demonstrated by the optimized nano-conflation, indicating that prolixity modifies the flyspeck's face area and periphery and that the drug is released by a disintegration process. First order was used to study the drug release medium (Figure 8). Direct retrogression to determine the value of n is the only way to determine whether or not the pattern of release follows Fickian prolixity. The release pattern will follow Fickian prolixity if n = 0.45. The release pattern exhibits non-Fickian prolixity if n is between 0.45 and 0.89, suggesting that prolixity and corrosion cooperate to control the release. It indicates Transport-2 super case or case-2 relaxation even if n is higher than 0.89. The release exponent(n) value of 0.075 for the phrasings showed that the release pattern was set up to follow non-Fickian prolixity, and the nano emulsion was found to follow first order.

Table 6: The table below summarizes the R^2 values for each kinetic model applied.

Percentage (v/v) of different components based on thermodynamic stability, an observation study							
Phase diagram	T80/PEG 200	oil	Smix	Aqueous	H/C	Cent	Freez. Thaw Cent:
A	1:01	10	70	20	✓	✓	✓
A	1:01	10	60	30	✓	✓	✓
A	1:01	10	50	40	✓	✓	×
A	1:01	10	40	50	×	-	-
B	2:01	10	70	20	✓	✓	✓
B	2:01	10	60	30	✓	✓	✓
B	2:01	10	50	40	✓	✓	✓
C	3:01	10	70	20	✓	✓	✓
C	3:01	10	60	30	✓	✓	✓
C	3:01	10	50	40	✓	✓	✓
C	3:01	10	40	50	×	-	-

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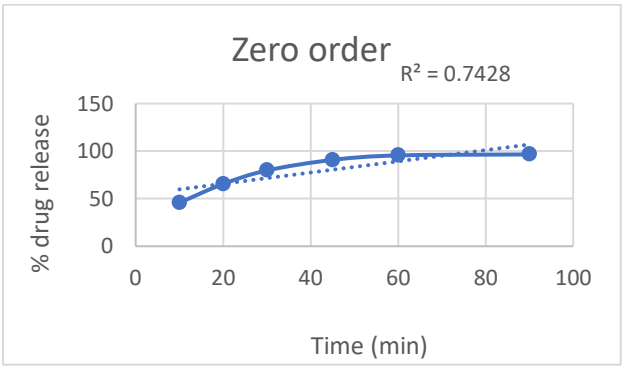

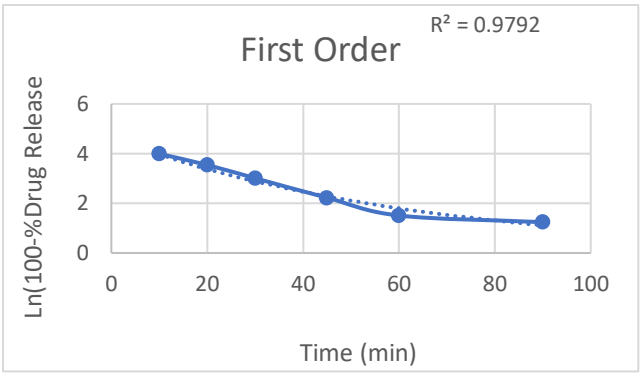

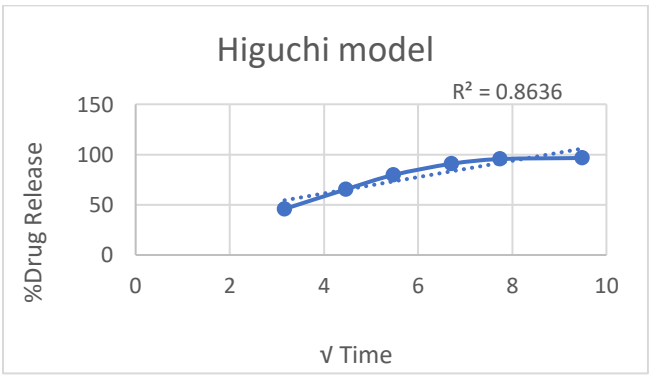

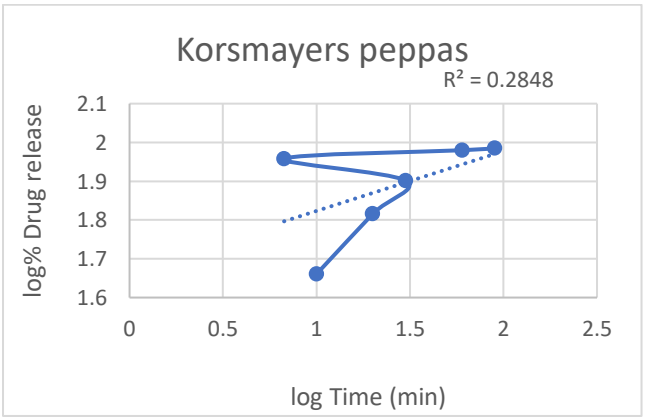

Kinetic Model	R^2 Value	Interpretation	Conclusion
Zero-order	0.7428	Constant release over time	Suggests a uniform release rate ideal for controlled drug delivery, but not the best fit here.
First-order	0.9792	Concentration-dependent release	Indicates that the release rate decreases as drug concentration declines.
Higuchi	0.8636	Diffusion-driven release	implies drug release is primarily controlled by diffusion through the matrix
Korsmeyer–Peppas	0.2848	Diffusion+ erosion/anomalous transport	Suggests a mixed mechanism involving both diffusion and erosion; useful for complex release profiles.

Journal of Chemical Health Risks

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Regression analysis revealed that the first order fit best (R^2= 0.9792), which is perfect for systems that release the active ingredient gradually over time.

Conclusion: Through ultrasonic emulsification, the current study effectively created and described a stable nano-emulsion formulation of rutin trihydrate using orange oil, Tween 80, and PEG 200. Clearness and uniformity were shown by the optimized nano-emulsion's high drug content (99.03±2.14%), tiny droplet size (58.0±0.27nm), polydispersity index (0.446), and high transmittance (99.78±0.03%). The electrostatic stability of the formulation was validated by the zeta potential value of -22.9 mV. The drug release kinetics followed the First Order, indicating a diffusion-controlled release mechanism, while in vitro drug release experiments showed significantly improved dissolution (79.67±0.23% in 30 minutes) in comparison to the pure marketed tablet formulation (46.75±0.35%). A promising this nano-emulsion technology offers a method for enhancing the oral bioavailability of drugs with poor water solubility, like rutin trihydrate.

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