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Comprehensive Preformulation, Formulation, and Stability Evaluation of Curcumin Nanoemulsion for Enhanced Bioavailability

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Highlights

• Quality by Design (QbD) approach was applied for curcumin nanoemulsion optimization.

• Optimized formulation (F9) demonstrated globule size of 138 nm, PDI 0.22, and zeta potential –36 mV.

• In vitro release demonstrated >99% curcumin release within 480 minutes.

• Stability confirmed at refrigerated storage over 3 months with no significant changes.

• Nanoemulsion enhances curcumin's solubility, dissolution, and oral bioavailability.[1,3,8]

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Curcumin; Nanoemulsion; D rug Release; Stability Study; Bioavailability; Box–Behnken Design

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Abstract

Background: Curcumin, a polyphenolic compound from Curcuma longa, exhibits potent therapeutic effects but suffers from poor aqueous solubility, instability, and low oral bioavailability.[1,9,5]

Methods: A curcumin nanoemulsion was optimized using a Quality by Design (QbD) approach with Box–Behnken design. Thirteen formulations were prepared by high-shear homogenization and ultrasonication, and evaluated for globule size, PDI, zeta potential, viscosity, pH, refractive index, and in vitro drug release.[2,5,10]

Results: The optimized formulation (F9) demonstrated a globule size of 138 nm, PDI of 0.22, and zeta potential of –36 mV, ensuring stability and uniformity. In vitro release studies demonstrated >99% drug release within 480 minutes. Stability studies confirmed refrigerated conditions preserved integrity for three months.[3,9,18]

Conclusion: The optimized nanoemulsion enhanced curcumin solubility, dissolution, and stability, representing a promising oral delivery system for improved bioavailability and potential pharmaceutical and nutraceutical applications.[6,8,13]

Overall, the findings highlight that QbD-enabled optimization of curcumin nanoemulsion successfully enhanced solubility, dissolution, and stability, providing a promising oral delivery system to overcome curcumin's bioavailability challenges and supporting its potential translation into effective therapeutic and nutraceutical applications.[3,7,21]

1. Introduction

Curcumin, a hydrophobic polyphenolic compound isolated from the rhizome of *Curcuma longa* (turmeric), has attracted immense scientific attention owing to its broad spectrum of pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, and anticancer effects. It has been widely utilized in traditional medicine systems such as Ayurveda and Chinese medicine for centuries, and modern pharmacological studies continue to validate its therapeutic potential in chronic diseases including cancer, diabetes, cardiovascular disorders, and neurodegenerative conditions. Despite this wide range of pharmacological activities, curcumin's clinical application remains severely limited due to its poor aqueous solubility, low dissolution rate, rapid metabolism, and instability at physiological pH, all of which contribute to its extremely low oral bioavailability.[2,7,8]

Several formulation strategies have been explored to enhance the solubility and systemic availability of curcumin, including liposomes, solid lipid nanoparticles, polymeric nanoparticles, inclusion complexes, and phospholipid conjugates. Among these, nanoemulsions—thermodynamically stable colloidal dispersions consisting of oil, surfactant, co-surfactant, and aqueous phase—have emerged as a particularly promising approach. Their unique advantages include small droplet size (typically in the range of 20–200 nm), high surface area for drug dissolution, enhanced permeation through biological membranes, and improved physical stability compared to conventional emulsions. Furthermore, nanoemulsions are relatively easy to scale up using techniques such as high-shear homogenization and ultrasonication, making them commercially attractive drug delivery systems.[3,8,14]

In recent years, the application of Quality by Design (QbD) principles in pharmaceutical development has provided a systematic framework for identifying critical material attributes and process parameters that influence product quality. Statistical tools such as Box–Behnken design allow efficient optimization of multiple formulation variables, leading to reproducible and robust drug delivery systems. Incorporating QbD into nanoemulsion development ensures not only enhanced drug performance but also regulatory compliance and industrial feasibility.[1,9,19]

Given these considerations, the present study focuses on the development and optimization of a curcumin-loaded nanoemulsion using a QbD-driven approach. The formulated system was characterized for its physicochemical properties, in vitro release profile, and stability under different storage conditions. The ultimate goal is to enhance curcumin's oral bioavailability and therapeutic potential, thereby facilitating its translation from laboratory research to clinical and nutraceutical applications.[1,3,8]

2. Materials and Methods

2.1 Preformulation Studies

Table 1 presents the absorbance values used for constructing the calibration curve for curcumin.

Preformulation studies were carried out to establish the identity, purity, and fundamental physicochemical characteristics of curcumin prior to formulation into a nanoemulsion system. These studies are essential for selecting suitable excipients, predicting drug–excipient interactions, and designing a stable delivery system.[6,9,15]

2.1.1 Identification of Curcumin

The identity of curcumin was confirmed using multiple analytical techniques: TLC (Rf ~1.3), UV–Vis spectroscopy (λmax at 429 nm), FT-IR spectroscopy (O–H stretch at 3300 cm^{-1}, C=O stretch at 1650 cm^{-1}), and melting point determination (176–177 °C). All results matched literature values, confirming purity and authenticity.

2.1.2 Micromeritic and Flow Properties

Flow properties were measured to assess handling and processing feasibility. Curcumin powder showed an angle of repose of 30°, Carr's index of 15%, and Hausner ratio of 1.18, all of which indicate good flow properties suitable for formulation.

2.1.3 Solubility Studies

Curcumin was sparingly soluble in water (~11 ng/mL) but exhibited higher solubility in ethanol, methanol, acetone, and DMSO. It also showed good solubility in lipid-based carriers such as Eucalyptus oil, oleic acid, and essential oils, supporting the choice of a lipid-based formulation system.

2.1.4 Partition Coefficient

The partition coefficient (logP) of curcumin was determined using the octanol–water system. A logP value of ~3.0 was obtained, indicating its lipophilic nature. This suggests high affinity for lipid membranes but limited aqueous solubility, necessitating a nanoemulsion approach to enhance dissolution and absorption.

2.2 Formulation Development

The composition of all thirteen formulations (F1–F13) is detailed in Table 2.

Thirteen curcumin nanoemulsion formulations (F1–F13) were prepared and optimized using a Box–Behnken design. Independent variables included oil concentration (%), surfactant concentration (%), and homogenization speed (rpm). Dependent responses were globule size, PDI, and % drug release. The lipid phase contained curcumin, piperine, Compritol® 888, and Eucalyptus oil, while the aqueous phase contained STPP, sodium cholate, and Tween 80. High-shear homogenization followed by probe sonication was employed.[3,7,8,16]

2.3 Evaluation Parameters

Physicochemical and release studies were carried out to characterize formulations:

- Globule size and PDI by Dynamic Light Scattering (DLS).
- Zeta potential using electrophoretic light scattering.
- Viscosity with Brookfield viscometer.
- pH using digital pH meter.
- Refractive index by Abbe refractometer.

- In vitro drug release using USP basket apparatus with an egg membrane model. Samples were analyzed spectrophotometrically at 429 nm, and release kinetics were modeled using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

3. Results and Discussion

The nanoemulsion formulations significantly improved curcumin's solubility and dissolution profile. Among the 13 formulations, F9 was identified as optimal with a droplet size of 138 nm, PDI of 0.22, and zeta potential of –36 mV. This confirmed uniformity, nanoscale size, and excellent stability. The in vitro release profile showed ~99.6% release at 480 min, compared to negligible release from pure curcumin suspension.

3.1 Globule Size and PDI

The physicochemical evaluation parameters for all formulations are summarized in Table 3.

Globule size ranged from 138–270 nm across formulations, with F9 showing the smallest size (138 nm). PDI values ranged 0.22–0.54, with F9 exhibiting the most uniform distribution.

3.2 Zeta Potential

Zeta potential values ranged between –25 and –36 mV. The optimized F9 formulation showed –36 mV, indicating strong repulsion and colloidal stability.

3.3 pH and Viscosity

The pH values ranged from 5.5 to 7.0, within acceptable limits for oral formulations. Viscosity varied from 15–50 cP, with F9 showing 20 cP, supporting good flow and ease of administration.

3.4 In Vitro Drug Release

The cumulative drug release data for formulation F9 and comparative formulations are presented in Table 3 (Drug Release Summary).

Formulation F9 exhibited the highest release, with nearly complete release (>99%) within 480 minutes. Release kinetics indicated diffusion-controlled release with contributions from lipid matrix erosion.

The in vitro release profile of F9 was analyzed using four kinetic models: zero-order, first-order, Higuchi, and Korsmeyer–Peppas. The initial phase (0–75 min) exhibited a linear increase in drug release, fitting the zero-order model with a rate constant k0≈1.06 /min}, indicating a constant release rate from the matrix. However, the full release curve showed better alignment with the first-order model, where the logarithmic transformation of the unreleased fraction yielded a rate constant k≈0.0148 minsuggesting concentration-dependent release kinetics.

The Higuchi model, applied to the early release region (0–45 min), demonstrated strong linearity between cumulative release and the square root of time, with a release constant kH≈8.50 %/min, confirming diffusion-controlled behavior. Additionally, the Korsmeyer–Peppas model applied to the same early region (15–45 min) yielded a release exponent n=1.0462n = 1.0462 and rate constant k=0.0113k = 0.0113, indicating super Case II transport, typically associated with

polymer relaxation or swelling mechanisms.

Together, these findings suggest that while the release begins with diffusion-dominated kinetics, it transitions into a more complex mechanism involving matrix relaxation or erosion. The high value of n (>1) supports the presence of non-Fickian transport, making the Korsmeyer–Peppas model particularly relevant for describing the release behavior of F9.

3.5 Refractive Index

The refractive index of formulations ranged from 1.38–1.71. F9 showed the lowest RI (1.38), supporting nanoscale droplet dispersion and optical transparency.

3.6 Stability Study

The stability results of optimized formulation F9 under different storage conditions are shown in Table 4.

Stability testing of F9 over three months at 4 °C, 25 °C/60% RH, and 40 °C/75% RH revealed refrigerated storage maintained stability. At 25 °C, minor creaming occurred after 2–3 months, while accelerated conditions (40 °C/75% RH) led to turbidity, size increase, and phase separation. This confirmed that cold storage is ideal for long-term stability.

4. Conclusion and Future Perspectives

The QbD-enabled curcumin nanoemulsion developed in this study successfully enhanced solubility, dissolution, and stability of curcumin. Formulation F9, with optimal droplet size, narrow PDI, high zeta potential, and excellent release profile, emerged as the best candidate. Stability studies confirmed refrigerated storage as the most suitable condition. These findings demonstrate the feasibility of curcumin nanoemulsion as a platform for improving oral bioavailability and therapeutic efficacy.

Future perspectives include in vivo pharmacokinetic and pharmacodynamic evaluations, scaling up for industrial production, and exploring integration into oral dosage forms such as capsules and functional foods for pharmaceutical and nutraceutical applications.

5. Tables and Figures

Table 1. Absorbance of Curcumin

Concentration (mcg/mL)	Absorbance
2	0.191
4	0.311

6	0.431
8	0.521
10	0.601

Table 2. Formulation Composition (F1–F13)

Run	Eucalyptus Oil (%)	Surfactant (%)	Homogenization Speed (rpm)	Curcumin (g)	STPP (g)	Piperine (g)	Sodium Cholate (g)	Compritol (g)	Water (%)
1	4	1	7500	1	0.5	0.2	0.3	0.8	95
2	8	1	7500	1	0.5	0.2	0.3	0.8	91
3	4	2	7500	1	0.5	0.2	0.3	0.8	94
4	8	2	7500	1	0.5	0.2	0.3	0.8	90
5	4	1	12500	1	0.5	0.2	0.3	0.8	95
6	8	1	12500	1	0.5	0.2	0.3	0.8	91
7	4	2	12500	1	0.5	0.2	0.3	0.8	94
8	8	2	12500	1	0.5	0.2	0.3	0.8	90
9	6	1.5	10000	1	0.5	0.2	0.3	0.8	92.5
10	6	1.5	10000	1	0.5	0.2	0.3	0.8	92.5
11	6	1.5	10000	1	0.5	0.2	0.3	0.8	92.5
12	6	1.5	10000	1	0.5	0.2	0.3	0.8	92.5
13	6	1.5	10000	1	0.5	0.2	0.3	0.8	92.5

Table 3. Physicochemical Evaluation of Formulations

Formulation	Globule Size (nm)	PDI	Zeta Potential (mV)	pH / Viscosity (cP)
F1	250	0.54	-28	6.2 / 48
F2	150	0.38	-35	6.0 / 18
F3	270	0.28	-30	6.5 / 37
F4	270	0.29	-35	5.5 / 15
F5	180	0.39	-29	6.3 / 39
F6	145	0.32	-30	7.0 / 50
F7	190	0.25	-32	5.5 / 40
F8	160	0.32	-25	6.4 / 47
F9	138	0.22	-36	6.5 / 20
F10	139	0.27	-34	6.9 / 25
F11	142	0.29	-30	6.7 / 28
F12	137	0.25	-29	6.5 / 22
F13	140	0.3	-34	6.9 / 20

Table 3. Drug Release Summary (F1–F13)

Detailed cumulative % release data are available; F9 demonstrated the highest release (>99% at 480 min), whereas other formulations showed lower cumulative release.

Time (min)	0	15	30	45	60	75	90	105	120	135	150
F9	0	18.9	41	59.3	74.4	83.5	91.8	95.3	97.5	98.4	99.2

				Time (min)	465	480				
				F9	99.9	99.9				
Time (min)	165	180	195	210	225	240	255	270	285	300
F9	99.3	99.2	99.3	99.4	99.6	99.6	99.7	99.9	99.9	99.9

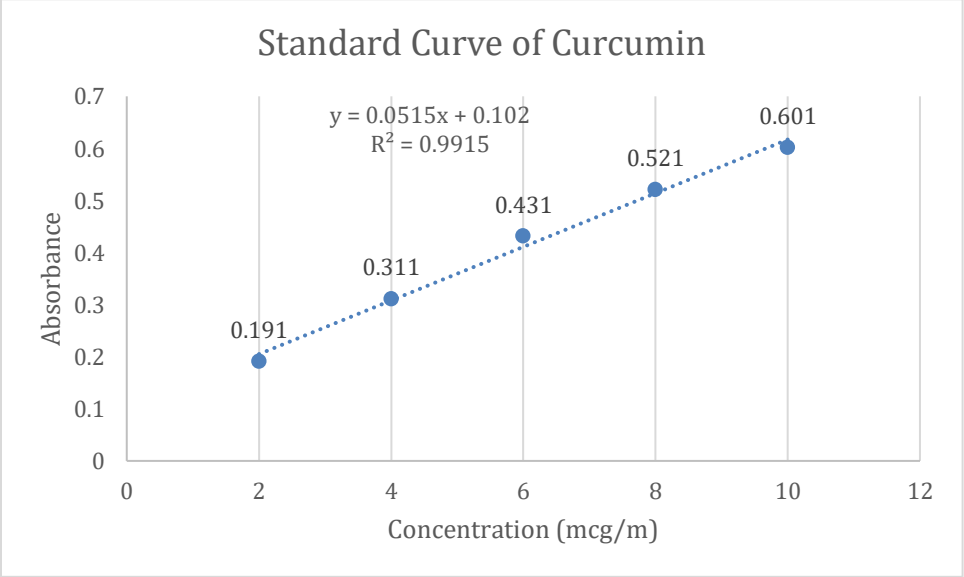
Time (min)	315	330	345	360	375	390	405	420	435	450
F9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9

Table 4. Stability Study of Optimized Formulation (F9)

Time Point	Storage Condition	Appearance	pH	Size (nm)	PDI	Zeta Potential / Content (%)
Initial	25°C / 60% RH	Clear	6.5	138.4	0.22	-36 / 99.9
1 month	25°C / 60% RH	No change	6.4	140.1	0.229	-34.7 / 98.6
1 month	4°C	Slight ↑ viscosity	6.6	139.5	0.217	-36 / 99.2
1 month	40°C / 75% RH	Slight turbidity	6.2	146.8	0.25	-30.4 / 96.4

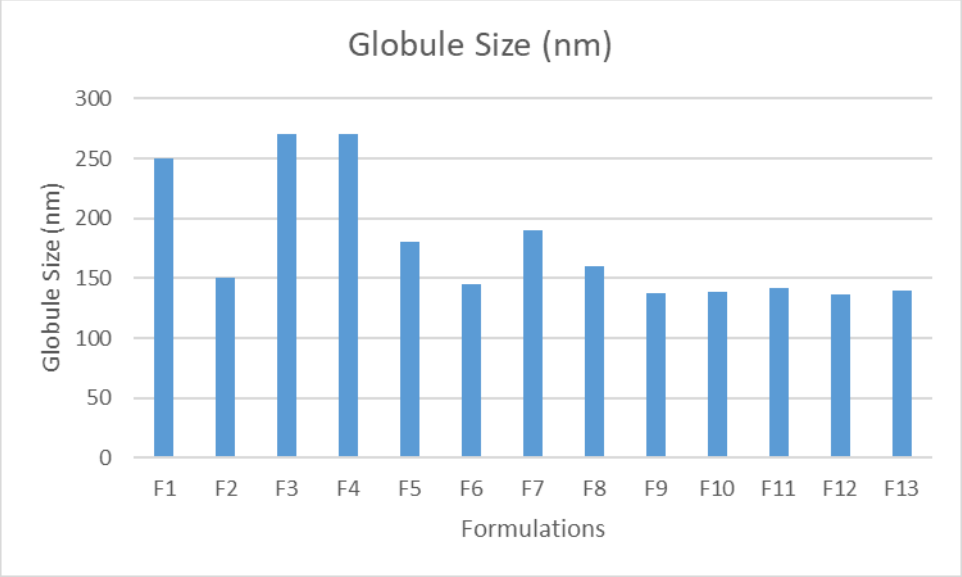
2 months	25°C	Minor creaming	6.3	143.3	0.245	-33.1 / 95.8
2 months	4°C	No change	6.5	140	0.221	-35.2 / 98.1
2 months	40°C	Creaming visible	6.0	154.6	0.285	-29.3 / 92.7
3 months	25°C	Slight sedimentation	6.2	149.2	0.26	-31.7 / 93.0
3 months	4°C	Slight ↑ size	6.5	142.5	0.24	-34.5 / 96.5
3 months	40°C	Phase separation	5.9	160.4	0.302	-27.5 / 88.4

1. Standard curve of Curcumin



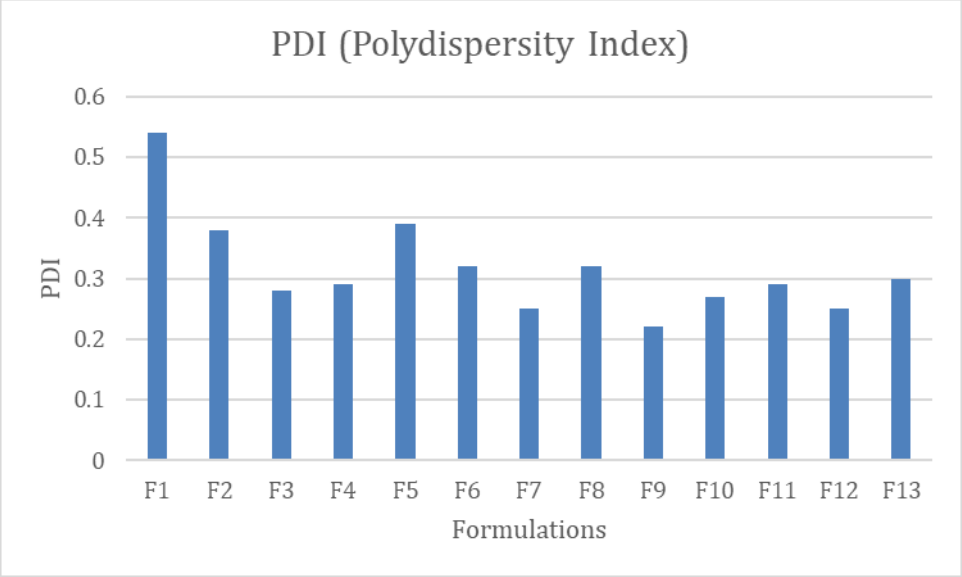
Graph 1.

2. Globule Size Distribution (F1–F13)



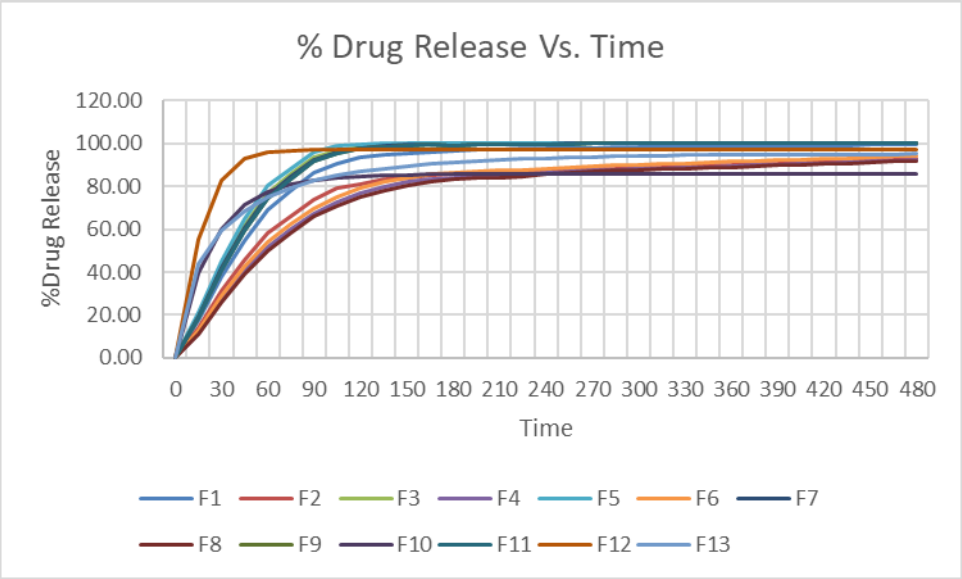
Graph 2.

2. Polydispersity Index (PDI) of Formulations (F1–F13)



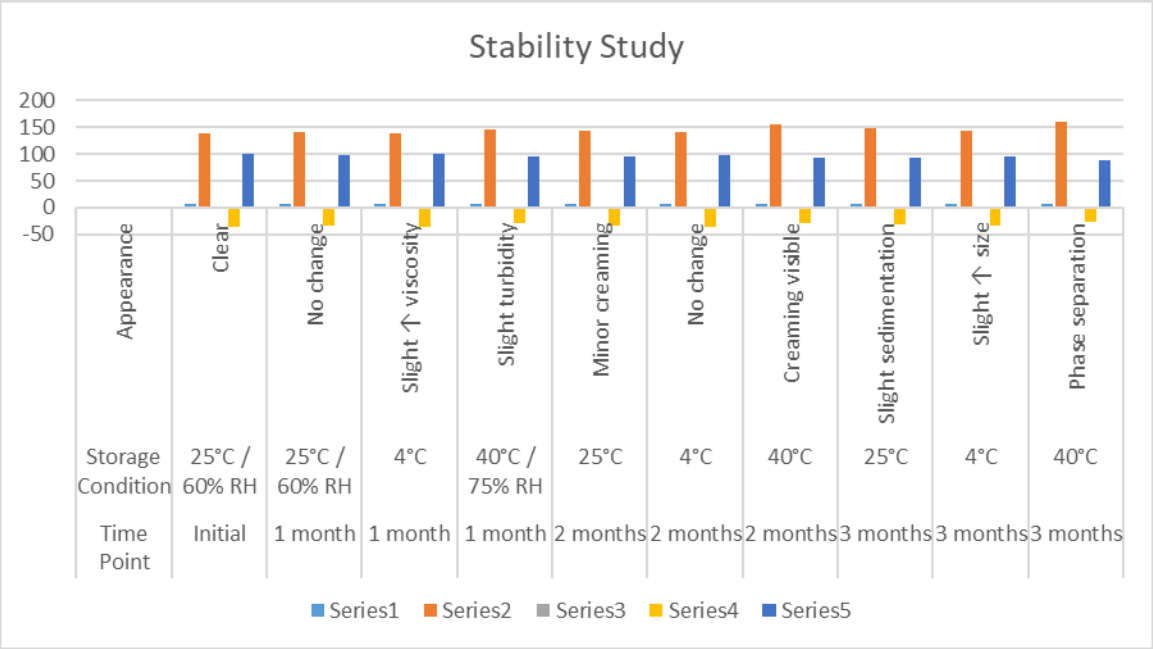
Graph 3.

4. In vitro Drug Release Profiles (F1–F13)



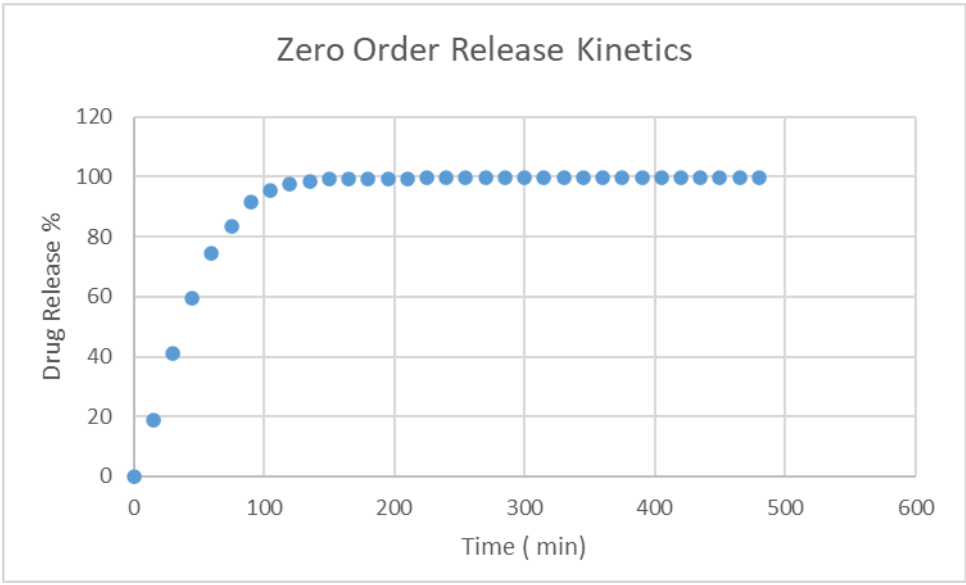
Graph 4.

5. Stability Trends of Optimized F9 (size, PDI, zeta potential across conditions/time)



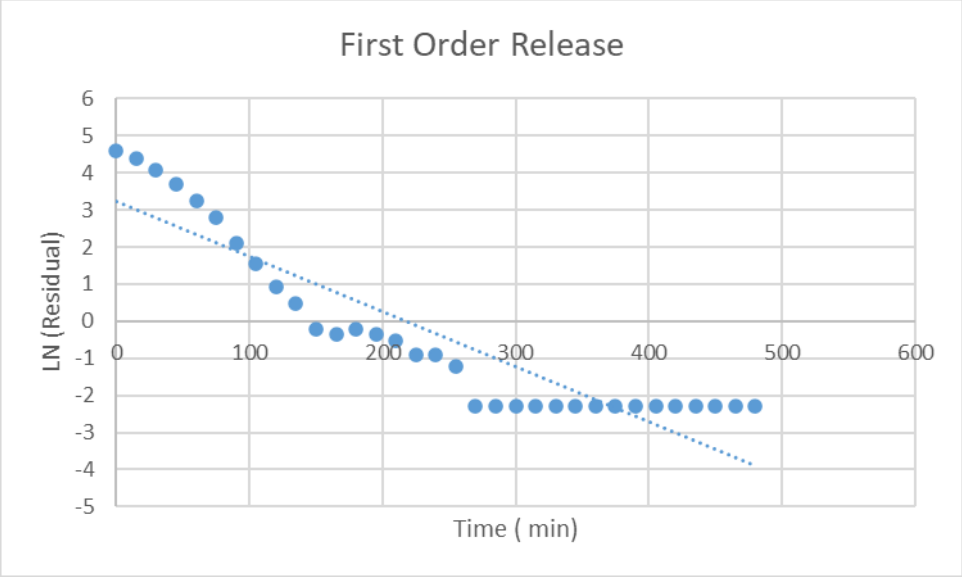
Graph 5.

6. Zero order Release Kinetics



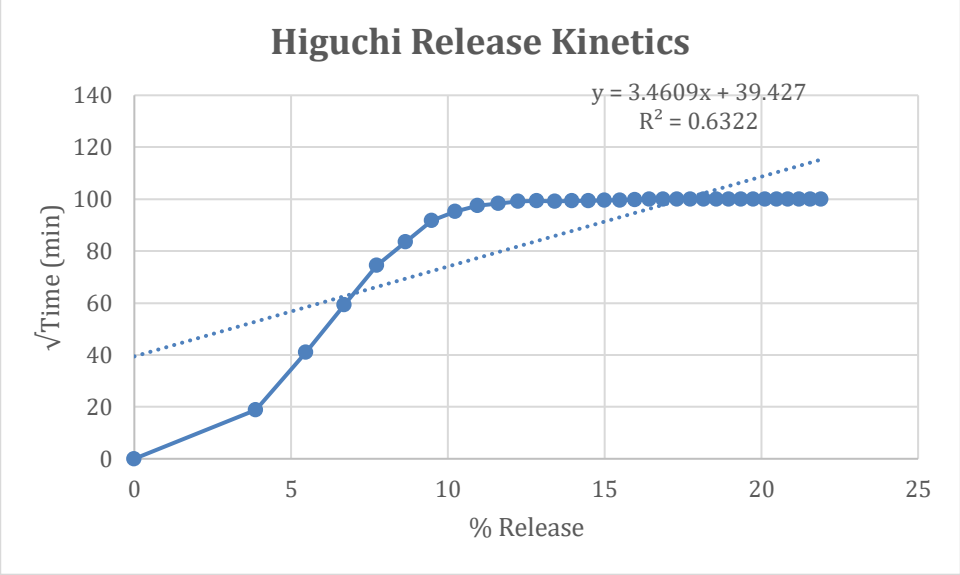
Graph 6.

7. First order Release Kinetics



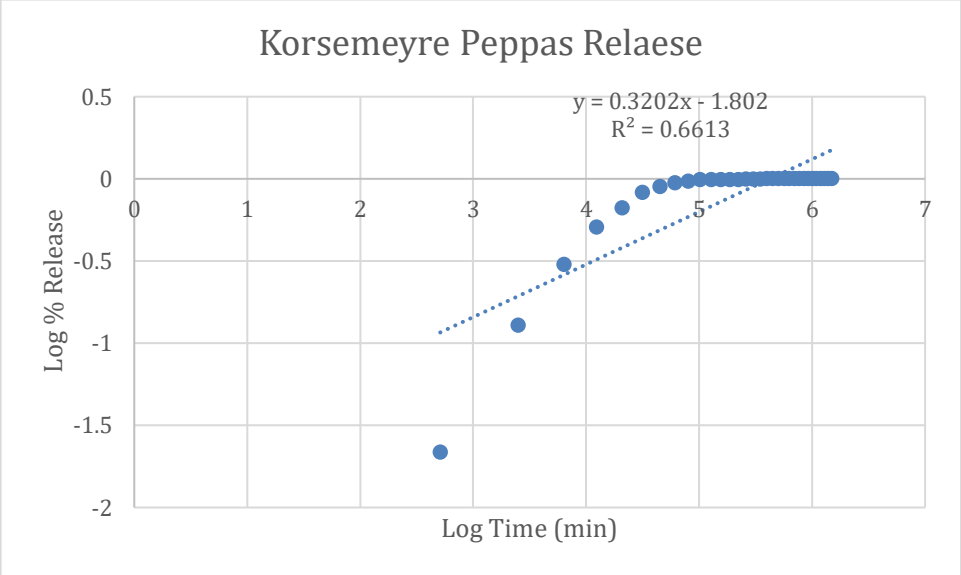
Graph 7.

8. Higuchi release kinetics



Graph 8.

9. Korsemeyre Peppas Relaese kinetics



Graph 9.

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Declarations

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Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Smita Srivastava: Conceptualization, Methodology, Investigation, Writing – original draft. Dr. Harinth Dwivedi: Supervision, Review & Editing. Dr. Rajiv Gupta: Validation, Data curation, Review & Editing.

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