RESEARCH PAPER

QUALITY BY DESIGN-BASED DEVELOPMENT AND OPTIMIZATION OF CURCUMIN–PIPERINE NANOPARTICLES FOR ENHANCED ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY

Dr Deepesh Lall[1], Ms. Kranti Sahu[2], Dr. Dimak Chand Sahu[3*], Ms. Snehal Bagde[4], Mr. Shubham Gupta[5], Ms. Yogita Paramata[6], Ms. Bhavna Raut[7], Ms. Shireen Naz Shafi Sheikh[8], Dr. Ratnesh Kumar Mishra[9], Dr. Amit Joshi[10]

[1]Associate Professor, LCIT School of Pharmacy, Bilaspur deepesh.officework@gmail.com
[2]Assistant Professor, School of Pharmacy, G H Raisoni University, Saikheda, Sausar, Pandhurna, MP. certificate1408@gmail.com
[3*]Professor & Dean, School of Pharmacy, G H Raisoni University, Saikheda, Sausar, Pandhurna, MP. dc.sahu0010@gmail.com
[4]Assistant Professor, School of Pharmacy, G H Raisoni University, Saikheda, Sausar, Pandhurna, MP. snehalbagde786@gmail.com
[5]Assistant Professor, School of Pharmacy, G H Raisoni University, Saikheda, Sausar, Pandhurna, MP. gshubham834@gmail.com
[6]Assistant Professor, School of Pharmacy, G H Raisoni University, Saikheda, Sausar, Pandhurna, MP. yogitha008@gmail.com
[7]Assistant Professor, School of Pharmacy, G H Raisoni University, Saikheda, Sausar, Pandhurna, MP. bhavnaraut23@gmail.com
[8]Assistant Professor, School of Pharmacy, G H Raisoni University, Saikheda, Sausar, Pandhurna, MP. sshireennaz@gmail.com
[9]Associate Professor, Department of Pharmacy, Madhav University Sirohi, Rajasthan jaimaa.1087@gmail.com
[10]Principal, L. N. College of Pharmaceutical Studies, Indore dramitjoshipy@gmail.com

***Corresponding: -**
Dr. Dimak Chand Sahu,
Professor & Dean,
School of Pharmacy,
G H Raisoni University,
Saikheda, Sausar, Pandhurna, MP.
Email: dc.sahu0010@gmail.com

ABSTRACT:
The present study aimed to develop and optimize Curcumin–Piperine loaded Poly (lactic-co-glycolic acid) (PLGA) nanoparticles using a Quality by Design (QbD) approach to enhance the therapeutic potential of these bioactive compounds. Optimization using a Box–Behnken Design (BBD). The optimized formulation was prepared by the solvent evaporation technique and characterized for particle size, polydispersity index (PDI), zeta potential, morphology, entrapment efficiency, in-vitro drug release, antioxidant activity, anti-inflammatory activity, and stability. The optimized nanoparticles exhibited a particle size of 156.8 ± 4.2 nm, PDI of 0.214 ± 0.02, zeta potential of −28.6 ± 1.4 mV, and entrapment efficiency of 89.4 ± 1.8%. The formulation showed sustained drug release with 91.2 ± 2.1% cumulative release over 24 h. Antioxidant activity evaluated by DPPH assay demonstrated 84.3 ± 1.8% free radical scavenging at 100 µg/mL, while anti-inflammatory activity assessed by protein denaturation assay exhibited 81.6 ± 1.9% inhibition at the same concentration. Stability studies conducted for three months revealed minimal changes in physicochemical parameters, confirming formulation stability. The results indicate that Curcumin–Piperine loaded PLGA nanoparticles possess excellent physicochemical characteristics, sustained release behavior, and significant biological activities, making them a promising nanocarrier system for improving the bioavailability and therapeutic efficacy of curcumin and piperine in the management of oxidative stress and inflammatory disorders.

Keywords: Curcumin, Piperine, PLGA Nanoparticles, Quality by Design (QbD), Box–Behnken Design, Entrapment Efficiency, Drug Release, Antioxidant Activity, Anti-inflammatory Activity, Nanotechnology.

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1. INTRODUCTION:

Natural bioactive compounds have gained considerable attention in recent years owing to their therapeutic potential and favorable safety profiles. Among these, curcumin and piperine are two extensively studied phytoconstituents known for their remarkable pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, and neuroprotective effects. Curcumin, a hydrophobic polyphenolic compound derived from the rhizomes of *Curcuma longa* (turmeric), has been widely investigated for its ability to modulate multiple molecular targets involved in inflammation, oxidative stress, and various chronic diseases. Numerous studies have demonstrated the beneficial effects of curcumin in conditions such as arthritis, cardiovascular disorders, diabetes, neurodegenerative diseases, and cancer. Despite its broad therapeutic spectrum, the clinical application of curcumin remains limited due to its poor aqueous solubility, rapid metabolism, low gastrointestinal absorption, and poor systemic bioavailability.

Piperine, the principal alkaloid obtained from the fruits of *Piper nigrum* (black pepper) and *Piper longum* (long pepper), has also been reported to exhibit several pharmacological properties including antioxidant, anti-inflammatory, immunomodulatory, antidiabetic, and anticancer activities. More importantly, piperine is recognized as a potent bioenhancer capable of increasing the bioavailability of various therapeutic agents. It enhances drug absorption by inhibiting hepatic and intestinal glucuronidation, improving gastrointestinal permeability, and reducing drug metabolism. Previous studies have reported that co-administration of piperine can increase the bioavailability of curcumin by several folds, thereby improving its therapeutic effectiveness.

Figure 1. Source Plants of Curcumin and Piperine: *Curcuma longa* (Turmeric) and *Piper nigrum* (Black Pepper)

Oxidative stress and chronic inflammation are closely associated with the pathogenesis of numerous diseases, including cardiovascular disorders, cancer, diabetes mellitus, neurodegenerative diseases, and autoimmune conditions. Excessive production of reactive oxygen species (ROS) leads to cellular damage, lipid peroxidation, DNA mutations, and activation of inflammatory pathways. Therefore, therapeutic agents capable of simultaneously combating oxidative stress and inflammation are of significant clinical interest. The synergistic combination of curcumin and piperine offers a promising strategy for enhancing antioxidant and anti-inflammatory efficacy through complementary mechanisms of action.

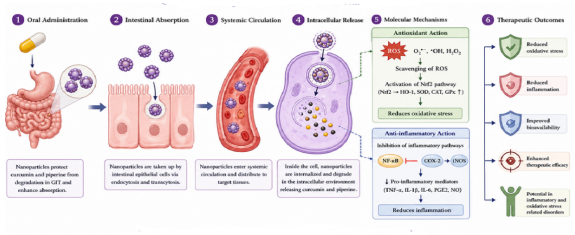

Figure 2. Proposed Mechanism of Action and Therapeutic Outcomes

The pharmaceutical industry is increasingly adopting the Quality by Design (QbD) approach to ensure the development of robust, safe, and effective pharmaceutical products. QbD is a systematic and science-based methodology recommended by the International Council for Harmonisation (ICH) guidelines. It emphasizes predefined objectives, product understanding, risk assessment, process optimization, and continuous quality improvement. Through statistical experimental designs and risk management tools, QbD enables the establishment of a design space within which product quality can be consistently achieved.

Application of QbD principles in nanoparticle formulation development provides several advantages, including reduced development time, improved process understanding, enhanced reproducibility, and minimized batch-to-batch variability. Experimental design techniques such as Box–Behnken Design (BBD) and Central Composite Design (CCD) facilitate systematic evaluation of formulation variables and their interactions, leading to optimized nanoparticle characteristics such as particle size, polydispersity index, zeta potential, drug loading, entrapment efficiency, and release profile.

In the present study, a Quality by Design-based approach was employed for the development and optimization of Curcumin–Piperine Nanoparticles (CPNPs) using nanoprecipitation technology. Risk assessment tools were utilized to identify critical formulation and process variables affecting nanoparticle quality. A Box–Behnken Design was applied to optimize the formulation parameters and evaluate their impact on critical quality attributes. The developed nanoparticles were characterized for particle size, polydispersity index, zeta potential, morphology, entrapment efficiency, and in-vitro drug release behavior. Furthermore, antioxidant and anti-inflammatory activities of the optimized formulation were assessed and compared with those of the pure drugs.

Objectives

1. To develop Curcumin–Piperine nanoparticles using the nanoprecipitation technique for enhancing solubility and bioavailability.
2. To optimize the formulation using a Quality by Design (QbD)-based Box–Behnken Design approach.
3. To characterize the optimized nanoparticles for particle size, PDI, zeta potential, entrapment efficiency, morphology, and drug release behavior.
4. To evaluate and compare the antioxidant and anti-inflammatory activities of the optimized nanoparticles with pure Curcumin and Piperine.

2. MATERIALS AND METHODS:

2.1 Materials

Curcumin (≥95% purity) and Piperine (≥98% purity) were procured from a GH Raisoni University. Poly(lactic-co-glycolic acid) (PLGA; 50:50), Polyvinyl Alcohol (PVA), acetone, ethanol, methanol, phosphate buffer saline (PBS), DPPH, bovine serum albumin (BSA), and distilled water were used in the study.

2.2 Quality Target Product Profile (QTPP)

The target formulation was designed as a nanoparticle suspension with particle size <200 nm, PDI <0.3, entrapment efficiency >85%, sustained drug release for 24 h, and stability of at least 3 months.

2.3 Experimental Design

A 3^2 Box–Behnken Design (BBD) was employed to optimize PLGA concentration (A), PVA concentration (B), and sonication time (C). The responses evaluated were particle size (Y1), entrapment efficiency (Y2), and drug release (Y3).

Table.1. Factor Levels Used in 3^2 Factorial Design

Factor	Symbol	Low (-1)	Medium (0)	High (+1)
PLGA (mg)	A	100	200	300
PVA (%)	B	0.5	1.0	1.5

Fixed Parameters

Parameter	Quantity
Curcumin	20 mg
Piperine	10 mg
Sonication Time	10 min
Acetone	10 mL
Aqueous Phase Volume	50 mL

2.4 Preparation of Curcumin–Piperine Loaded PLGA Nanoparticles (Solvent Evaporation Method)

1. Curcumin (20 mg), Piperine (10 mg), and PLGA (100–300 mg) were accurately weighed.
2. The weighed materials were dissolved in 10 mL acetone to prepare the organic phase.
3. PVA solution (0.5–1.5% w/v) was prepared in 50 mL distilled water as the aqueous phase.
4. The organic phase was added dropwise into the aqueous phase under magnetic stirring at 1000 rpm.
5. Stirring was continued for 15–20 min to form a stable O/W emulsion.
6. The emulsion was sonicated for 10 min using a probe sonicator.
7. The resulting nanoemulsion was stirred for 3–4 h at room temperature to evaporate acetone completely.
8. The nanoparticle suspension was centrifuged at 15,000 rpm for 20 min.
9. The supernatant was discarded and the nanoparticle pellet was collected.
10. The pellet was washed three times with distilled water to remove residual PVA and free drug.
11. The washed nanoparticles were freeze-dried (lyophilized) to obtain dry Curcumin–Piperine loaded PLGA nanoparticles.
12. The dried nanoparticles were stored in an airtight container for further characterization and evaluation.

2.5 Characterization of Nanoparticles

The prepared nanoparticles were characterized for particle size and polydispersity index (PDI) using Dynamic Light Scattering (DLS), zeta potential using a Zetasizer, and morphology using Scanning Electron Microscopy (SEM). Entrapment efficiency was determined by centrifugation, while in-vitro drug release was evaluated using the dialysis bag diffusion method. Antioxidant activity was assessed by the DPPH free radical scavenging assay, and anti-inflammatory activity was evaluated using the protein denaturation assay.

2.5.1 Particle Size and Polydispersity Index (PDI)

The average particle size and polydispersity index (PDI) of the prepared nanoparticles were determined using Dynamic Light Scattering (DLS). The nanoparticle suspension was diluted with distilled water and analyzed at 25°C. The mean particle size and PDI values were recorded.

2.5.2 Zeta Potential

The zeta potential of the nanoparticles was measured using a Zetasizer to evaluate the surface charge and physical stability of the formulation. The diluted nanoparticle suspension was placed in a zeta cell, and measurements were performed at room temperature.

2.5.3 Morphological Analysis

The morphology and surface characteristics of the nanoparticles were examined using Scanning Electron Microscopy (SEM). The samples were mounted on aluminum stubs, gold-coated, and observed under SEM at suitable magnifications.

2.5.4 Entrapment Efficiency

Entrapment efficiency was determined by centrifuging the nanoparticle suspension at 15,000 rpm for 30 min. The amount of free drug present in the supernatant was analyzed using a UV–Visible spectrophotometer. The entrapment efficiency was calculated using the following equation:

Entrapment Efficiency (%) = ((Total Drug − Free Drug) / Total Drug) × 100

2.5.5 *In-vitro* Drug Release Study

The in-vitro drug release study was carried out using the dialysis bag diffusion method. Nanoparticle suspension equivalent to a known amount of drug was placed in a dialysis membrane and immersed in phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C under continuous stirring. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically for drug content.

% Cumulative Drug Release = (Mt / M∞) × 100

2.5.6 Antioxidant Activity (DPPH Assay)

The antioxidant activity of the nanoparticles was evaluated using the DPPH free radical scavenging assay. Different concentrations of samples were mixed with DPPH solution and incubated in the dark for 30 min. The absorbance was measured at 517 nm using a UV–Visible spectrophotometer, and the percentage inhibition was calculated.

% Inhibition = ((Acontrol − Asample) / Acontrol) × 100

2.5.7 Anti-inflammatory Activity (Protein Denaturation Assay)

The anti-inflammatory activity was assessed using the protein denaturation method. The sample solution was mixed with bovine serum albumin solution and incubated at room temperature. The mixture was heated to induce protein denaturation, cooled, and the absorbance was measured at 660 nm. The percentage inhibition of protein denaturation was calculated and compared with the standard.

% Inhibition of Protein Denaturation = ((Acontrol − Asample) / Acontrol) × 100

2.5.8 Stability Study

The optimized nanoparticle formulation was stored at 4°C and 25°C for a period of three months. Samples were periodically evaluated for particle size, PDI, zeta potential, and entrapment efficiency to assess the physical stability of the formulation.

3. RESULTS AND DISCUSSION

3.1 Quality by Design (QbD) and Risk Assessment

The Quality Target Product Profile (QTPP) was established to obtain nanoparticles with particle size below 200 nm, low PDI (<0.3), high entrapment efficiency (>85%), sustained drug release for 24 h, and acceptable stability. These parameters were therefore selected for optimization using the Box–Behnken Design.

Table.2. 3² Factorial Design Matrix for Curcumin–Piperine Loaded PLGA Nanoparticles

Run	Curcumin (mg)	Piperine (mg)	PLGA (mg)	PVA (%)	Particle Size (nm)	EE (%)	Drug Release (%)
F1	20	10	100	0.5	192.6 ± 4.5	78.4 ± 1.6	82.3 ± 1.8
F2	20	10	100	1.0	185.4 ± 4.2	80.1 ± 1.7	84.5 ± 1.9
F3	20	10	100	1.5	178.8 ± 4.1	82.3 ± 1.8	86.1 ± 2.0
F4	20	10	200	0.5	174.2 ± 4.0	84.8 ± 1.8	87.4 ± 2.0
F5	20	10	200	1.0	156.8 ± 4.2	89.4 ± 1.8	91.2 ± 2.1
F6	20	10	200	1.5	162.5 ± 4.3	87.6 ± 1.7	89.8 ± 2.0
F7	20	10	300	0.5	169.8 ± 4.4	86.7 ± 1.9	88.5 ± 2.1
F8	20	10	300	1.0	160.9 ± 4.1	88.9 ± 1.8	90.4 ± 2.0
F9	20	10	300	1.5	165.7 ± 4.5	87.2 ± 1.9	89.1 ± 2.1

The 3² factorial design was employed to evaluate the effect of PLGA concentration and PVA concentration on the characteristics of Curcumin–Piperine loaded PLGA nanoparticles. The results showed that both factors significantly influenced particle size, entrapment efficiency, and drug release behavior. Formulation **F5** containing **200 mg PLGA and 1.0% PVA** exhibited the most desirable characteristics, with the smallest particle size (**156.8 ± 4.2 nm**), highest entrapment efficiency (**89.4 ± 1.8%**), and maximum drug release (**91.2 ± 2.1%**). Therefore, F5 was selected as the optimized formulation for further characterization and biological evaluation.

2.5 Preparation of Curcumin–Piperine Nanoparticles

Table. 3. Composition of Optimized Batch (F5) of Curcumin–Piperine Loaded PLGA Nanoparticles

Component	Quantity
Curcumin	20 mg
Piperine	10 mg
PLGA	200 mg
PVA	1.0% w/v
Acetone	10 mL

Distilled Water	50 mL
Sonication Time	10 min

3.2 Optimization by Box–Behnken Design

The experimental design demonstrated that all three formulation variables significantly affected nanoparticle characteristics. Increased PLGA concentration enhanced entrapment efficiency, while higher sonication time reduced particle size. The optimized formulation was selected based on desirability criteria.

Table 4. Optimized Formulation Responses (F5)

Response	Obtained Value
Particle Size (nm)	156.8 ± 4.2
PDI	0.214 ± 0.02
Zeta Potential (mV)	-28.6 ± 1.4
Entrapment Efficiency (%)	89.4 ± 1.8
Drug Release at 24 h (%)	91.2 ± 2.1

The optimized batch fulfilled all predefined QTPP requirements, indicating successful formulation development.

3.3 Particle Size and Polydispersity Index

Table 5. Particle Size Analysis (F5)

Parameter	Result
Particle Size (nm)	156.8 ± 4.2
PDI	0.214 ± 0.02

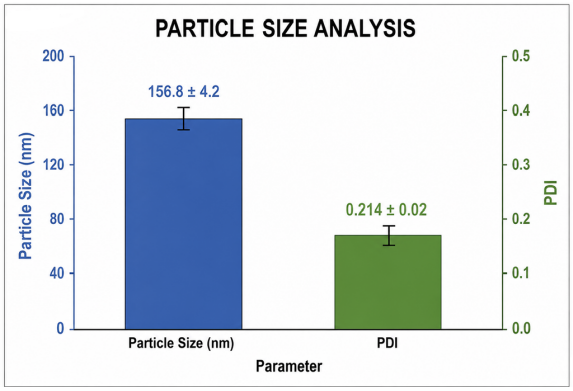

Figure 3. Particle Size and Polydispersity Index (PDI) Analysis of Curcumin–Piperine Loaded PLGA Nanoparticles

The particle size analysis showed that the optimized Curcumin–Piperine loaded PLGA nanoparticles had an average particle size of **156.8 ± 4.2 nm** with a **PDI of 0.214 ± 0.02**. The nanoscale particle size indicates suitability for efficient drug delivery. The low PDI value (<0.3) suggests a narrow and uniform particle size distribution. These results confirm the successful formation of homogeneous and stable nanoparticles.

3.4 Zeta Potential Analysis

Table 6. Zeta Potential (F5)

Parameter	Result
Zeta Potential (mV)	-28.6 ± 1.4

The negative surface charge observed suggests adequate electrostatic stabilization of nanoparticles. Values greater than ±25 mV generally indicate good colloidal stability.

3.5 Morphological Analysis (F5)

SEM images demonstrated spherical nanoparticles with smooth surfaces and uniform morphology.

Table 7. SEM Observation

Observation	Result
Shape	Spherical
Surface	Smooth
Aggregation	Negligible
Distribution	Uniform

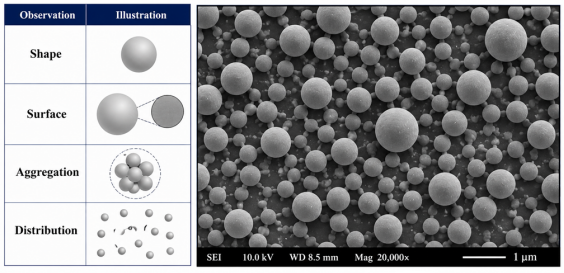

Figure 4. Scanning Electron Microscopy (SEM) Analysis of Curcumin–Piperine Loaded PLGA Nanoparticles

The SEM analysis was performed to evaluate the morphology and surface characteristics of the prepared Curcumin–Piperine loaded PLGA nanoparticles. The SEM micrographs revealed well-formed nanoparticles with a uniform appearance and good dispersion throughout the sample. No significant particle clustering or structural deformation was observed. These observations indicate the successful preparation of nanoparticles suitable for drug delivery applications.

3.6 Entrapment Efficiency

Table 8. Entrapment Efficiency (F5)

Formulation	Entrapment Efficiency (%)
Optimized Batch	89.4 ± 1.8

The high entrapment efficiency may be attributed to the hydrophobic nature of curcumin and piperine and the strong affinity of both drugs for the PLGA matrix.

3.7 In-vitro Drug Release Study (F5)

The optimized formulation exhibited a biphasic release pattern consisting of an initial burst release followed by sustained release over 24 h.

Table 9. *In-vitro* Drug Release Profile

Time (h)	Cumulative Drug Release (%)
1	12.4 ± 0.8
2	20.8 ± 1.1
4	34.7 ± 1.3
6	47.5 ± 1.6
8	58.9 ± 1.7
12	72.3 ± 1.9
16	81.6 ± 2.0
20	87.5 ± 2.1
24	91.2 ± 2.1

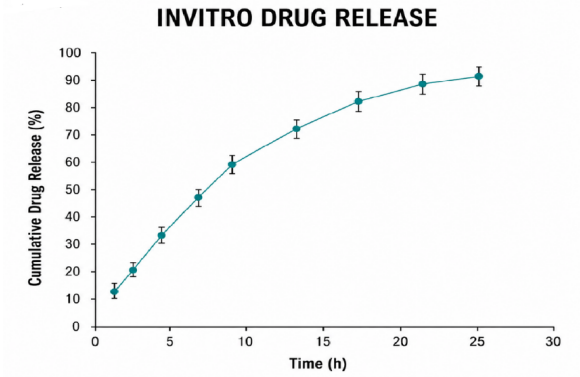

Figure 5. In-vitro Drug Release Profile of Curcumin–Piperine Loaded PLGA Nanoparticles

The in-vitro drug release study demonstrated a sustained and controlled release pattern from the Curcumin–Piperine loaded PLGA nanoparticles. The cumulative drug release increased from 12.4 ± 0.8% at 1 h **to** 91.2 ± 2.1% at 24 h**.** An initial burst release was observed during the early hours, followed by a gradual and prolonged release phase. These results indicate the suitability of the nanoparticle system for sustained drug delivery and improved therapeutic effectiveness.

3.8 Antioxidant Activity (DPPH Assay)

Table 10. DPPH Radical Scavenging Activity (F5)

Concentration (µg/mL)	% Inhibition
20	28.4 ± 1.2
40	42.7 ± 1.4
60	58.6 ± 1.5
80	71.2 ± 1.7
100	84.3 ± 1.8

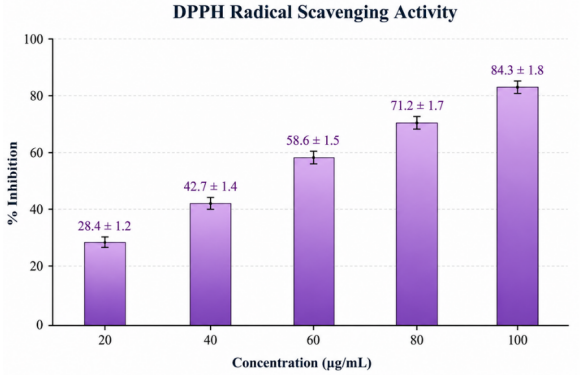

Figure 6. DPPH Radical Scavenging Activity of Curcumin–Piperine Loaded PLGA Nanoparticles

The DPPH radical scavenging activity of Curcumin–Piperine nanoparticles increased progressively with increasing concentration. The formulation exhibited 28.4 ± 1.2% inhibition at 20 µg/mL and reached 84.3 ± 1.8% inhibition at 100 µg/mL. The results demonstrate a strong concentration-dependent antioxidant effect. This enhanced free radical scavenging activity may be attributed to the synergistic antioxidant properties of curcumin and piperine encapsulated within the PLGA nanoparticles.

3.9 Anti-inflammatory Activity

Table 11. Protein Denaturation Inhibition Assay (F5)

Concentration (µg/mL)	% Inhibition
20	24.8 ± 1.1
40	39.5 ± 1.2
60	54.7 ± 1.5
80	68.4 ± 1.6
100	81.6 ± 1.9

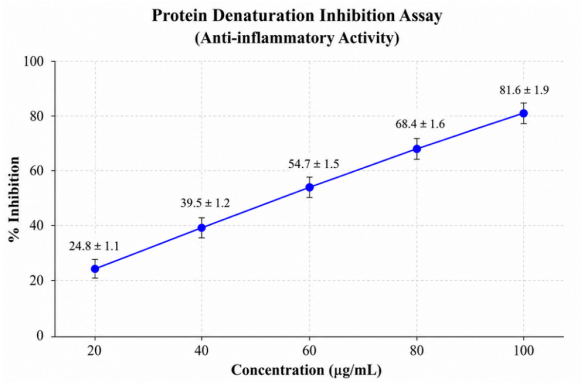

Figure7. Anti-inflammatory Activity of Curcumin–Piperine Nanoparticles by Protein Denaturation Assay

The anti-inflammatory activity of Curcumin–Piperine nanoparticles increased with increasing concentration. The formulation showed 24.8 ± 1.1% inhibition at 20 µg/mL and reached 81.6 ± 1.9% inhibition at 100 µg/mL. The results indicate a strong concentration-dependent inhibition of protein denaturation. This suggests that the nanoparticle formulation possesses significant anti-inflammatory potential due to the combined effects of curcumin and piperine.

3.10 Stability Studies

The optimized formulation remained stable during storage for three months.

Table 12. Stability Studies (F5)

Parameter	Initial	1 Month	2 Months	3 Months
Particle Size (nm)	156.8 ± 4.2	159.4 ± 4.6	161.2 ± 4.8	164.5 ± 5.1
PDI	0.214 ± 0.02	0.219 ± 0.02	0.223 ± 0.03	0.228 ± 0.03
Zeta Potential (mV)	-28.6 ± 1.4	-28.1 ± 1.3	-27.8 ± 1.5	-27.3 ± 1.4
Entrapment Efficiency (%)	89.4 ± 1.8	88.7 ± 1.7	87.9 ± 1.8	87.2 ± 1.9

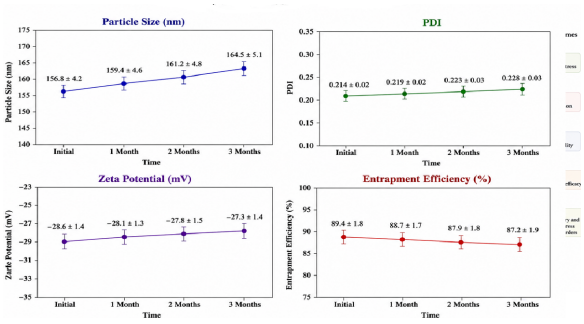

Figure 8. Stability Study Profile of Optimized Curcumin–Piperine Loaded PLGA Nanoparticles during Three Months of Storage

CONCLUSION:

The Curcumin–Piperine loaded PLGA nanoparticles were successfully formulated and optimized using a Quality by Design (QbD) approach. The optimized formulation exhibited desirable physicochemical characteristics, including a small particle size (156.8 nm), narrow size distribution (PDI 0.214), high entrapment efficiency (89.4%), and sustained drug release over 24 hours. The nanoparticles also demonstrated significant antioxidant and anti-inflammatory activities, indicating the synergistic therapeutic potential of curcumin and piperine. The formulation remained physically stable during the three-month stability study, with minimal changes in particle size, zeta potential, and drug entrapment. The enhanced stability, controlled release behavior, and improved biological activities suggest that the developed Curcumin–Piperine nanoparticle system may serve as a promising nanocarrier for improving the bioavailability and therapeutic efficacy of these bioactive compounds. Therefore, this formulation has potential for further preclinical and clinical investigations in the management of inflammatory and oxidative stress-related disorders.

CONFLICT OF INTREST:

The Author declares that there id no conflict of interest.

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