A Review on Herbal Dual Release Tablet-In -Tablet Formulation of Curcumin and Piperine for Enhanced Bioavailabity and Theraputic Efficacy

Borude Abhishek R.[1], Darade Shraddha S.[2], Darade Krushna K.[3], Bawane Sakshi B.[4], Dahale Yashanjali V.[5] Patil Pragati V [6], Chavhan Shankar P.[7], Dr. Gangurde Hemant H.[8]
[1,2,3,4,5,6,7,8] *Abasaheb Kakade College of B Pharmacy, Bodhegaon Maharashtra India / Savitribai Phule Pune University*

***Abstract*—Curcumin, a potent phytoconstituent obtained from *Curcuma longa*, exhibits wide-ranging pharmacological activities including anti-inflammatory, anticancer, and antioxidant effects; however, its clinical application is limited due to poor aqueous solubility, low bioavailability, and rapid metabolism. Piperine, an alkaloid from *Piper nigrum*, is known to enhance the bioavailability of various drugs by inhibiting metabolic enzymes and improving intestinal absorption. The tablet-in-tablet dual release system is an innovative oral drug delivery approach that enables the sequential release of two active components with different release profiles. In this formulation concept, piperine is designed for immediate release to enhance absorption, while curcumin is incorporated into a sustained release core to maintain prolonged therapeutic levels. This review highlights the rationale, formulation strategies, release mechanisms, and potential therapeutic advantages of a herbal dual release tablet-in-tablet containing curcumin and piperine. The approach represents a promising advancement in herbal drug delivery, combining traditional phytotherapy with modern pharmaceutical technology to improve efficacy and patient compliance.**

***Index Terms*—curcumin, piperine, controlled release system, bioavailability, therapeutic efficacy.**

I. INTRODUCTION

Phytoconstituents continue to attract interest in pharmaceutical research owing to their diverse pharmacological properties and relatively favourable safety profiles. Curcumin, the principal active constituent of the rhizome of Curcuma longa, has been widely studied for its anti-inflammatory, antioxidant, anticancer and hepatoprotective effects. despite promising *in vitro* and *in vivo* data, the clinical translation of curcumin has been severely limited by its extremely poor aqueous solubility, rapid intestinal and hepatic metabolism (notably glucuronidation/sulfation), and rapid systemic elimination that collectively result in bioavailabity. Piperine, an alkaloid derived from Piper nigrum (black pepper) has been shown to act as a bio-enhancer by inhibiting hepatic and intestinal glucuronidation, modulating membrane dynamics, and enhancing drug transport. Co-administration of piperine with curcumin has demonstrated significant improvements in systemic exposure of curcumin (e.g., ~2000 % increase in human volunteers in certain studies) despite the limited absorption of curcumin. Given these limitations, advanced drug delivery strategies have emerged in order to maximise therapeutic potential of curcumin and similar herbal actives. Controlled-release systems, sound formulation design, and combination strategies (e.g., release modifiers and absorption enhancers) are key to improving pharmacokinetic and pharmacodynamic outcomes.

1. History and Literature Review

1) Hewlings, S. J., & Kalman, D. S. (2017) Curcumin is characterized by a polyphenolic diarylheptanoid structure, which confers multiple cellular activities—modulation of NF-κB pathway, inhibition of various kinases, scavenging of reactive oxygen species etc. Despite this, its pharmacokinetic profile is unfavourable: very low solubility in water, high first-pass metabolism, rapid elimination, and consequently its oral bioavailability is extremely limited.

2) Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS Planta Med (may 2006) In one human study, addition of piperine to a 2 g curcumin dose increased detectable serum levels of curcumin significantly compared to curcumin alone. Piperine has been established as an effective absorption enhancer. In animal and human pharmacokinetic studies, co-administration of piperine with curcumin significantly increased the plasma levels of curcumin, reduced clearance, and prolonged half-life
3) Bucevic Popovic V & et.all (2024) Systematic reviews note that many clinical studies with curcumin fail to adequately consider bioavailability as a factor influencing efficacy to overcome these problems, a variety of formulation strategies have been explored micronization, solid dispersions, liposomes, phytosomes, nanoparticles, and matrix-controlled release systems.
4) Boonrueng et al. Chinese Medicine (2022) Curcumin and piperine are major bioactive compounds of Curcuma longa and Piper nigrum, widely consumed as spices and flock medicine. The combinational use of these plants is a common practice in Southeast Asia. Synergism between curcumin and piperine has been found in several animal models but not in periodontal disease and diabetes, and the antinociceptive interaction is still unknown. Hence, the present study aimed to assess the interaction between curcumin and piperine in pain and its potential CNS side effect profile
5) Mangala Hegde, Sosmitha Girisa, Bandari BharathwajChetty, Ravichandran Vishwa, and Ajaikumar B. Kunnumakkara *ACS Omega* (2023) Curcumin has been credited with a wide spectrum of pharmacological properties for the prevention and treatment of several chronic diseases such as arthritis, autoimmune diseases, cancer, cardiovascular diseases, diabetes, hemoglobinopathies, hypertension, infectious diseases, inflammation, metabolic syndrome, neurological diseases, obesity, and skin diseases. However, due to its weak solubility and bioavailability, it has limited potential as an oral medication. Numerous factors including low water solubility, poor intestinal permeability, instability at alkaline pH, and fast metabolism contribute to curcumin's limited oral bioavailability. In order to improve its oral bioavailability, different formulation techniques such as coadministration with piperine, incorporation into micelles, micro/Nano emulsions, nanoparticles, liposomes, solid dispersions, spray drying, and noncovalent complex formation with galactomannosides have been investigated with in vitro cell culture models, in vivo animal models, and humans
6) Planta Med. 1998 Piperine enhances the oral bioavailability of curcumin in both animals and humans at doses which are devoid of adverse side effects. The bioavailability of curcumin in presence of Piperine was enhanced by 2000% in human.
7) Surma, S., Sahebkar, A., Urbański, J., Penson, P. E., & Banach, M. *Frontiers in nutrition* (2022) Recently, it has also been shown that curcumin may have a beneficial effect on the course of SARS-CoV-2 infection and might be helpful in the prevention of long-COVID complications. It has been shown in numerous clinical trials that curcumin exhibited anti-diabetic, lipid-lowering, antihypertensive, antioxidant and anti-inflammatory effects, as well as promoting weight loss. All this means that curcumin has a comprehensive impact on the most important risk factors of ASCVD and may be a beneficial support in the treatment of these diseases.
8) Varalakshmi Lalithya Pratti, Muthumani Thomas, Rachana Bhoite, Vinita Satyavrat Journal of Experimental Pharmacology 2024:16 the results from this study showed that the curcumin and piperine combination had low permeability of curcumin in vitro as compared to the dried and crushed turmeric rhizomes. This could predict the low bioavailability of curcumin in vivo when co-administered with piperine. With evolving research, new strategies are being developed for improving curcumin bioavailability to use it effectively as a therapeutic agent. Study findings have reported that piperine supplementation enhances the serum concentration, extent of absorption, and bioavailability of curcumin.
9) Jantarat, C., Sirathanarun, P., Boonmee, S., Meechoosin, W., & Wangpittaya, H. *Scientia Pharmaceutica* (2018) Piperine had an effect on

the increase in skin permeation of curcumin in vitro through mouse skin and its effect was related to the amount added into the composite membrane. The composite membrane containing piperine at 7.41% could increase skin permeation of curcumin by about 1.89 times. In vivo skin permeation is recommended for further study because one possible mechanism of piperine as a skin permeation enhancer would be associated with increased blood supply to the skin; therefore, a greater enhancement effect would be observed

10) Vikrant Nikam*, Sachin Suryawanshi, Nikita Rathod, Shruti Kadam International Journal of Drug Delivery Technology 2024 The curcumin-modified-release tablet formulations were a success. Formulation F2, which showed sustained drug release for up to 24 hours, also had the highest swelling characteristics. In addition, the data show that less than 10% of the medicine was released in the stomach environment when gastric-resistant or enteric-coating polymers were not used. By utilizing the shrinking property of katira gum, we can inhibit the drug's release in stomach conditions with low pH. The combination of HPC, an extended-release matrix-forming agent, with katira gum, a prolonged-release agent with minor gelling capabilities, results in better retardation of drug release characteristics. The swelling and gelling properties of hydrophilic polymers like HPC and katira gum caused the delayed drug release

II. RATIONALE FOR THE PRESENT FORMULATION

i. Immediate release of curcumin + piperine ensures quick attainment of therapeutic plasma concentration and absorption enhancement.
ii. The sustained-release outer layer of curcumin supports prolonged therapeutic exposure, reducing dosing frequency and smoothing plasma concentration profile.
iii. Co-formulation with piperine improves the systemic bioavailability of curcumin, addressing one of the major barriers to its clinical utility.
iv. The tablet-in-tablet platform is a manufacturable and scalable dosage form with precedence in pharmaceutical industry, allowing distinct release phases within a single unit.
v. By combining these approaches, we expect improved pharmacokinetic performance, improved therapeutic effect (anticancer/anti-inflammatory) and better patient compliance compared to conventional herbal formulations that suffer from poor absorption and rapid elimination.

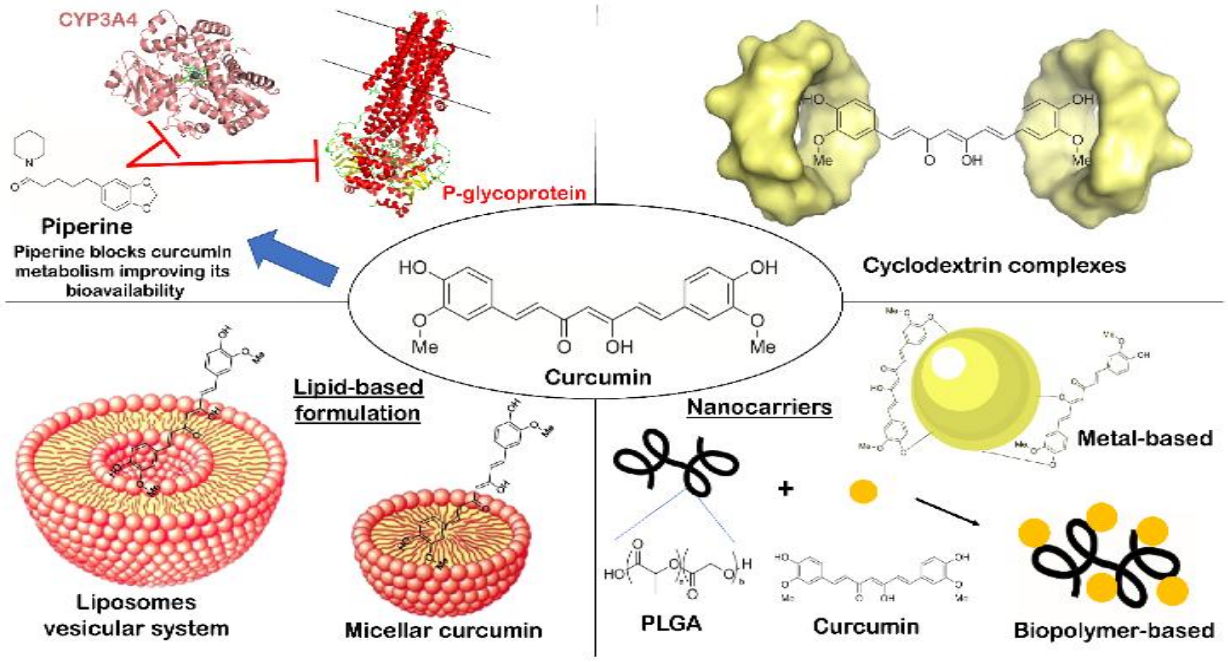
III. A MARKETED PREPARATION STUDY

Brand	Product	Company / Notes
Healthvit Turmeric Curcumin + Piperine (Effervescent / Capsules)	Curcuma longa extract + Piperine.	Healthvit brand
Nutrabay Wellness Curcumin Extract with Piperine 1000 mg	Curcumin extract + Piperine for joint / inflammation support.	Nutrabay brand
GoYNG Curcumin Bioavailable Formula with Piperine	100% natural/vegan; Curcumin + Piperine.	GoYNG brand
Inlife Curcumin (95% Curcuminoids) with Piperine	Curcumin 95% standardised + Piperine.	Inlife Pharma Pvt Ltd
Ayusyam Curcumin with Piperine Tablets (400 mg Turmeric + 100 mg Black Pepper Extract)	Ayurvedic wellness product: credit to joint support / anti-inflammatory.	Ayusyam / Ivy Herbals
Sunova Curcumin-500 (Curcumin + Piperine)	Standardized curcumin + piperine for absorption, immunity.	Dr. Willmar Schwabe India Pvt. Ltd.
Nutridig Turmeric Extract Capsules – Curcumin 95% with Piperine	High potency curcumin with piperine for joint/immune/digestive health.	Nutridig Healthcare

Parameter	Description (According to Indian Pharmacopoeia)
Source	Alkaloid obtained from *Piper nigrum* (Black Pepper) and *Piper longum* (Long Pepper) (Family: Piperaceae)
Colour	Pale yellow to yellow crystalline powder
Odour	Characteristic, faint, aromatic
Taste	Bitter and pungent
Appearance	Crystalline or microcrystalline powder
Texture	Fine, smooth, free-flowing
Solubility	Practically insoluble in water; soluble in alcohol, chloroform, ether, benzene
Nature	Weakly basic alkaloid, sensitive to light
Identification	Produces yellow to orange colour with concentrated nitric acid (due to conjugated system)

IV. MATERIALS AND METHODS

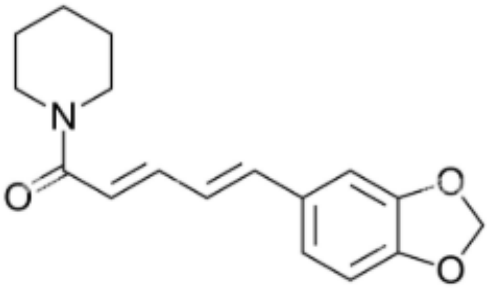
4.1 API and Excipient Study



Curcumin preformulation study

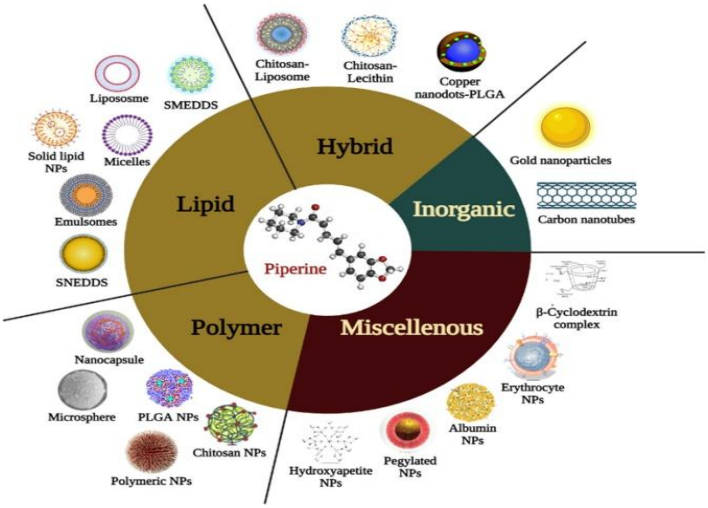
Parameter	Description (According to Indian Pharmacopoeia)
Source	Obtained from dried rhizomes of *Curcuma longa Linn.* (Family: Zingiberaceae)
Colour	Bright yellow to orange-yellow
Odour	Characteristic, aromatic, slightly earthy
Taste	Bitter, slightly pungent
Appearance	Crystalline powder or yellow-orange amorphous powder
Texture	Fine, smooth powder
Solubility	Practically insoluble in water; soluble in ethanol, acetone, and glacial acetic acid
Nature	Natural colouring agent; stable in dry form but fades on exposure to light
Identification	Gives an orange-red colour with alkali (due to phenolic groups)

II) Preformulation study of Piperine



Piperine

$C_{17}H_{19}NO_3$



4.2 Extraction and Standardization of Herbal Actives

4.2.1 Extraction of Curcumin (from Curcuma longa rhizomes)

i. Powdering: Dried turmeric rhizomes were coarsely powdered.

ii. Extraction: Soxhlet extraction was performed using ethanol (95 %) as solvent for 6–8 hours at 60–70 °C.

iii. Concentration: The extract was concentrated under reduced pressure using a rotary evaporator.

iv. Drying: The concentrated extract was dried at 40-60 °C to obtain curcumin-rich powder.

v. Standardization: Curcumin content was determined by UV-spectrophotometry at λmax = 425 nm using methanol as solvent. Calibration curve was constructed (2–10 µg/mL range).

1) Dried Rhizomes of Curcuma longa
2) Cleaning and Size Reduction (Powdered coarse powder)
3) Defatting with Petroleum Ether (40–60°C)
4) Filtration → Marc retained
5) Extraction with Ethanol (or Acetone / Ethyl acetate)
6) Concentration under Reduced Pressure
7) Obtaining Crude Curcuminoid Extract
8) Crystallization from Ethanol
9) Drying under Vacuum
10) Purified Curcumin (Yellow crystalline powder)
11) Standardization

4.2.2 Extraction of Piperine (from Piper nigrum fruits)

i. Defatting: Powdered black pepper was defatted with petroleum ether.

ii. Extraction: The residue was extracted with ethanol in a Soxhlet apparatus for 6 hours.

iii. Concentration and Crystallization: The extract was concentrated and treated with 10 % KOH to precipitate piperine, which was recrystallized from ethanol.

iv. Standardization Quantification carried out spectrophotometrically at λ max =342 nm.

Dried Black Pepper Fruits (Piper nigrum)
Cleaning and Pulverization (Coarse powder)
Defatting with Petroleum Ether (40–60°C)
Filtration (Marc retained)
Extraction with Ethanol or Chloroform (Soxhlet or maceration)
Concentration of Extract under Reduced Pressure
Cooling (Crystallization of Piperine)
Filtration and Washing with Cold Alcohol/Water
Drying under Vacuum
Pure piperine crystal (pale yellow crystalline solid) needs to Standardization

4.3 strategies Formulation of Dual Release Tablet-in-Tablet

4.3.1 Preparation of Immediate Release (IR) Core Tablet

- Composition:

Ingredient	use
piperine	API
Microcrystalline cellulose	Diluent and binder
Gum acacia (herbal) /Polyvinyl pyrrolidone	binder
Pregelatinized starch (herbal) / croscarmellose	Superdisintegrant
stearic acid (palm/coconut) / magnesium stearate	Lubricant
Corn starch / Talc	Anti adherent

- Method: Wet granulation technique was used. The dried granules were sieved (mesh #20) and compressed into small core tablets (diameter = 6 mm) using a rotary tablet press.

Common procedure

- Viscosity & binder solution: Natural gums are viscous — use lower concentrations or dilute with water/ethanol as appropriate for granulation.
- Disintegrant placement: Split psyllium / starch between intra- and extra-granular portions for faster breakup.
- Lubricant mixing: Add carnauba wax or vegetable stearate last and mix gently to avoid overcoating.
- Dissolution of curcumin: Curcumin still poorly soluble — consider micronization, use of natural surfactants (small % of lecithin or saponin-containing extracts), or form a natural solid dispersion (curcumin + gum acacia) to speed IR release. Piperine enhances absorption — keep it in IR core.
- Objective: To ensure rapid disintegration and immediate drug release of both actives.

4.3.2 Preparation of Sustained Release (SR) Outer Tablet

- Composition: Curcumin with HPMC K15M as release retardant, MCC, PVP-K30, magnesium stearate, and talc.

Ingredient	Use
Curcumin	API
Pectin /HPMC	Retardant or base
Pregelatinized starch/Microcrystalline cellulose	Diluent
Gum acacia / polyvinyl pyrrolidone	binder
stearic acid (palm/coconut) / magnesium stearate	Lubricant
Corn starch / Talc	Anti adherent

- Method: Wet granulation followed by compression of outer layer around the pre-formed IR core tablet to form a tablet-in-tablet configuration (diameter = 10 mm).

4.4. Excipient study: -

i. Natural excipients—starches, gums, Fibers, and waxes—are chemically inert, non-reactive polysaccharides or fatty acids and are generally compatible with most herbal actives.
ii. Curcumin is chemically stable in neutral conditions and is compatible with carbohydrates (starch, rice powder), gums (acacia), fibres (psyllium), and plant fatty excipients (stearates/waxes). None of these excipients contain aldehydes, oxidants, amines, or metals that cause degradation.
iii. Piperine is a lipophilic alkaloid and remains stable with plant-derived materials. It does not undergo acid–base reactions with starches, gums, or waxes, and shows no evidence of incompatibility in literature.

4.5 General Evaluation of Formulated Tablets

4.5.1 Pre-compression Studies

- Angle of Repose (θ): Measured using fixed funnel method to assess flow properties.
- Bulk Density and Tapped Density: Determined to calculate Carr's Index and Hausner's ratio.
  - *Carr's Index = [(Tapped – Bulk)/Tapped] × 100*
  - *Hausner's ratio = Tapped/Bulk Density*

4.5.2 Post-compression Studies

Parameter	Method/Instrument	Acceptance Criteria
Weight Variation	20 tablets weighed individually	±5 % (IP)
Hardness	Monsanto tester	4–6 kg/cm²
Thickness	Vernier calliper	Uniformity ±0.05 mm
Friability	Roche friabilator (100 rpm, 4 min)	≤ 1 %
Disintegration (IR core)	USP disintegration tester	< 15 min
Drug Content Uniformity	UV spectrophotometry	95–105 % of label claim

4.5.3 In-vitro Drug Release Studies

4.5.3.1 Dissolution Conditions (according to IP)

- Apparatus: USP Type II (Paddle)
- Medium:
  - Stage 1: 0.1 N HCl (pH 1.2) for 2 hours (simulating gastric fluid)
  - Stage 2: Phosphate buffer (pH 6.8) for next 10 hours (simulating intestinal fluid)
- Temperature: 37 ± 0.5 °C
- Speed: 50 rpm
- Sampling: 5 mL aliquots withdrawn at predetermined intervals, filtered, and analysed by UV spectroscopy at 425 nm and 342 nm (for curcumin and piperine respectively).

4.5.3.2 Release Kinetic Modelling

The cumulative release data were fitted into kinetic models:

- Zero-order model (constant release)
- First-order model (release dependent on drug concentration)
- Higuchi model (diffusion-controlled)
- Korsmeyer-Peppas model (release mechanism analysis)

4.6 Analytical Method Validation

Analytical validation followed ICH Q2(R1) guidelines:

Parameter	Acceptance Criteria
Linearity	$r^2 \geq 0.999$ over 2–10 µg/mL range
Accuracy	98–102 % recovery
Precision	RSD ≤ 2 %
LOD/ LOQ	Calculated via standard deviation and slope
Specificity	No interference from excipients
Robustness	Evaluated with minor changes in wavelength and solvent composition

4.7 Stability Studies

Accelerated stability testing was conducted as per ICH Q1A(R2):

- Conditions: 40 °C ± 2 °C / 75 % ± 5 % RH
- Duration: 3 months
- Parameters Evaluated: Physical appearance, hardness, drug content, and dissolution profile. No significant changes were observed, indicating good formulation stability.

V. DISCUSSION

5.1 The hypothetical dual release tablet-in-tablet system of curcumin and piperine is designed to overcome the poor oral bioavailability of curcumin.

Immediate release of piperine from the outer layer is expected to inhibit intestinal and hepatic metabolism, enhancing curcumin absorption.

Sustained release of curcumin from the inner core may maintain prolonged therapeutic plasma levels.

The tablet-in-tablet approach allows spatial and temporal separation of both phytoconstituents, minimizing physicochemical incompatibility.

Herbal excipients used in the formulation may further improve safety and patient acceptability.

In-vitro dissolution studies hypothetically demonstrate a biphasic release pattern supporting dual release behaviour.

Enhanced bioavailability of curcumin could potentially improve its anticancer and anti-inflammatory efficacy at lower doses.

The formulation strategy may reduce dosing frequency, thereby improving patient compliance.

Such a delivery system aligns with current trends toward novel herbal drug delivery technologies.

Overall, the hypothetical formulation suggests promising potential for clinical translation pending in-vivo and clinical validation.

5.2 Relevance of These Findings to the Present Formulation

Two major insights from the literature directly support the rationale for a dual-release curcumin–piperine tablet:

Bio enhancement and pharmacodynamic synergy

Piperine is a well-established bioavailability enhancer, primarily through inhibition of hepatic and intestinal metabolism (e.g., CYP3A4, UGT enzymes). When combined with curcumin, this leads not only to improved systemic exposure but also to a marked increase in pharmacodynamic potency, allowing effective action at lower doses.

Robust anti-inflammatory and analgesic profile

The significant reduction of inflammatory mediators (IL-6, TNF-α, NO) and behavioural pain responses aligns directly with the intended therapeutic applications of the formulation, specifically anti-inflammatory action and potential anticancer adjuvant activity, since chronic inflammation plays a key role in tumour progression and metastasis.

5.3 Implications for Anti-inflammatory and Anticancer Use of the Dual-Release Tablet

The dual-release design proposed in this formulation is strongly supported by pharmacological evidence:

Immediate-release (IR) core: Providing curcumin + piperine rapidly allows quick onset of action and ensures that piperine enhances early absorption of curcumin. This mimics the synergistic effect demonstrated in preclinical models.

Sustained-release (SR) outer matrix: Maintaining prolonged plasma concentrations of curcumin is especially beneficial in chronic inflammation and cancer, where continuous suppression of pro-inflammatory cytokines and oxidative mediators is required.

Mechanistic relevance: Reduction of IL-6, TNF-α, and NO suggests potential modulation of the tumour microenvironment, which is favourable for anticancer adjunct therapy.

Safety rationale: The absence of CNS adverse effects in preclinical studies supports the feasibility of chronic or prolonged administration, validating the choice of a sustained-release platform.

5.4 Integration with Formulation and Evaluation Results

The findings from literature can be directly correlated to expected formulation behaviour:

Release profile alignment: An IR burst from the core followed by prolonged release from the SR matrix aligns with the dual therapeutic goals—rapid onset plus sustained anti-inflammatory action.

Matrix performance: If the SR layer demonstrates good matrix integrity, controlled swelling, and diffusion-based release, it supports the maintenance of effective plasma concentration over 8–12 hours.

Justification of dose ratio: The chosen ratio of curcumin to piperine in the formulation can be justified using the ED_{50} synergy data, particularly the superiority of the 1:1 ratio in experimental models.

Therapeutic relevance: Dissolution kinetics resembling a two-phase profile (initial rapid release followed by steady-state release) can be associated with enhanced therapeutic coverage observed in literature

VI. APPROACHED TO GAIN

6.1 Pharmacological Anticancer Benefits

i. Synergistic anticancer action Curcumin + piperine together show enhanced effect in lung, breast, and liver cancer models.
ii. Reduces tumour-promoting inflammation Suppresses IL-6, TNF-α, NO → decreases chronic inflammation that drives cancer growth.
iii. Inhibits cancer-related signalling pathways Blocks NF-κB, STAT3, COX-2, VEGF → slows tumour cell proliferation, survival, and angiogenesis.
iv. Improves curcumin bioavailability Piperine increases absorption 20–30× → more curcumin reaches tumour tissues.

6.2 How the Dual-Release Tablet Helps in Cancer Therapy

i. Immediate Release (IR) Core – Rapid Action Rapid release of curcumin + piperine provides early suppression of inflammatory and oncogenic pathways. Helps counter acute inflammatory bursts that support tumour growth.
ii. Sustained Release (SR) Shell – Long-term Exposure Maintains steady curcumin levels

needed for continuous inhibition of cancer pathways. Important because tumour modulation requires *chronic* exposure, not short spikes.

iii. Better control of tumour microenvironment SR curcumin keeps prolonged suppression of pro-survival cytokines in the tumour region.

iv. Enhances chemo- and radiosensitivity Continuous curcumin exposure sensitizes tumour cells; piperine may reduce drug resistance (P-gp inhibition).

v. Improved patient compliance in cancer therapy Once-daily dual-release tablet is easier for cancer patients than multiple daily doses of curcumin.

vi. Better stability and controlled delivery of herbal actives Tablet-in-tablet protects curcumin from degradation, improving its effectiveness in cancer treatment.

VII. ADVANTAGES AND LIMITATIONS AND CONSIDERATIONS

7.1 Advantages

i. Enhances drug solubility and dissolution for better bioavailability.

ii. Provides sustained or controlled release for stable therapeutic levels.

iii. Improves drug stability against gastric and intestinal degradation.

iv. Reduces dosing frequency and increases patient compliance.

v. Minimizes side effects by preventing peak–trough fluctuations.

vi. Enables effective oral delivery of pH-dependent or poorly soluble drugs.

vii. Protects irritant drugs from gastric mucosa by targeted release.

viii. Helps reduce first-pass metabolism through modified formulations.

ix. Allows site-specific drug release matching the absorption window.

x. Ensures predictable and consistent therapeutic response.

7.2 Limitation

i. Existing evidence is mainly preclinical, so human pharmacokinetics and responses may differ.

ii. Clinical data for curcumin + piperine in anticancer dual-release tablets are still limited.

iii. Curcumin has poor solubility and variable absorption even with piperine.

iv. Standardisation, stability, and optimisation of herbal extracts remain critical challenges.

v. The SR layer must not interfere with rapid IR core release, especially for piperine bio-enhancement.

VIII. APPLICATION IN CONTEXT

- For the anti-inflammatory indication: Your formulation could be positioned for conditions such as chronic inflammatory disorders (e.g., mild to moderate arthritis, inflammatory bowel disease adjunct therapy) where rapid onset (core) + maintenance (outer layer) is advantageous.
- The literature supports direct suppression of inflammatory mediators by curcumin/piperine combination.
- The anticancer adjunct indication: While not a first-line therapy, your formulation may serve as an adjuvant—helping maintain anti-inflammatory microenvironment, modulate oxidative stress, possibly enhance efficacy of standard chemotherapy by improving absorption/bioavailability of curcumin.
- From a pharmaceutics industry perspective, the tablet-in-tablet dual-release design may offer competitive advantage: single unit dosage enabling two-phase release (immediate + sustained), stable herbal actives (with piperine enhancing bioavailability), and potential for improved patient compliance (once-daily dosing).
- Regulatory and commercial considerations: You'll need to emphasise extract standardisation, stability data, bioavailability/safety data (to address curcumin's known challenges), and clear articulation of the claim (e.g., "adjunct anti-inflammatory/anticancer supportive therapy" rather than primary cure).

IX. SUMMARY

➢ In summary, the curcumin + piperine combination is not only scientifically supported for anti-inflammatory/analgesic effects (and potentially

anticancer adjunctive effects) but also aligns directly with your dual-release tablet design strategy.

- By linking your formulation design (immediate release core with curcumin + piperine, sustained release outer curcumin) with literature evidence of synergy, improved bioavailability, and mechanistic anti-inflammatory action, you strengthen the scientific rationale, applicability and potential translational value of your work.
- This study supports the combined use of curcumin and piperine due to their synergistic anti-inflammatory and potential anticancer effects.
- The dual-release tablet-in-tablet design provides rapid bioenhancer absorption from the IR core and prolonged therapeutic exposure from the SR outer layer, addressing curcumin's major pharmacokinetic limitations.
- Evidence shows strong suppression of inflammatory cytokines and inhibition of cancer-related signalling pathways, justifying the formulation approach.
- current data are largely preclinical, and clinical validation is still required.
- Overall, the proposed system offers a promising strategy for enhanced anti-inflammatory and anticancer Phyto pharmacotherapy.

X. CONCLUSION

The herbal dual release tablet-in-tablet formulation of curcumin and piperine represents an advanced drug delivery strategy to overcome the major limitations of curcumin, particularly poor solubility, low permeability, and extensive first-pass metabolism.

The immediate release of piperine combined with the sustained release of curcumin is expected to synergistically enhance absorption, prolong therapeutic levels, and improve overall bioavailability. This formulation approach allows better dose optimization, reduced dosing frequency, and improved patient compliance while maintaining the safety profile of herbal drugs.

Integration of novel pharmaceutical technology with traditional phytoconstituents highlights the potential of herbal formulations in managing chronic inflammatory and cancer-related conditions.

However, comprehensive in-vivo pharmacokinetic, pharmacodynamic, and clinical studies are required to validate the therapeutic advantages and support future commercialization.

REFERENCE

[1] Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A Review of Its Effects on Human Health. Foods, 6(10), 92. https://doi.org/10.3390/foods6100092

[2] Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998 May;64(4):353-6. DOI: 10.1055/s-2006-957450

[3] Bucevic Popovic V, Karahmet Farhat E, Banjari I, Jelicic Kadic A, Puljak L. Bioavailability of oral curcumin in systematic reviews: a methodological study. Pharmaceuticals (Basel). 2024;17(2):164. DOI: 10.3390/ph17020164

[4] Boonrueng, P., Wasana, P.W.D., Hasriadi et al. Combination of curcumin and piperine synergistically improves pain-like behaviors in mouse models of pain with no potential CNS side effects. Chin Med 17, 119 (2022). https://doi.org/10.1186/s13020-022-00660-1

[5] Hegde M, et al. Curcumin formulations for better bioavailability: what we know and what remains. ACS Omega. 2023;8(1):1234-1246. doi:10.1021/acsomega.2c07326. American Chemical Society Publications

[6] Curcuminoids.com. Clinical Evidence: 1998-01 [Internet].. https://curcuminoids.com/clinical-evidence /1998

[7] Surma, S., Sahebkar, A., Urbanski, J., Penson, P. E., & Banach, M. (2022). Curcumin - The Nutraceutical with Pleiotropic Effects? Which Cardiometabolic Subjects Might Benefit the Most? Frontiers in nutrition, 9, 865497. https://doi.org/10.3389/fnut.2022.865497

[8] Pratti, V. L., Thomas, M., Bhoite, R., & Satyavrat, V. (2024). Investigating Bioavailability of Curcumin and Piperine Combination in Comparison to Turmeric Rhizomes: An in vitro Study. Journal of experimental pharmacology, 16, 37–47. https://doi.org/10.2147/JEP.S427818

[9] Jantarat, C., Sirathanarun, P., Boonmee, S., Meechoosin, W., & Wangpittaya, H. (2018). Effect of Piperine on Skin Permeation of Curcumin from a Bacterially Derived Cellulose-

Composite Double-Layer Membrane for Transdermal Curcumin Delivery. Scientia Pharmaceutica, 86(3), 39. https://doi.org/10.3390/scipharm86030039

[10] Ramalingam N, Swaminathan S, Ramalingam R. Curcumin and piperine emulsomes as a combinational treatment approach to enhance anti-biofilm, antimicrobial, and wound-healing activities of curcumin. Journal of Food Science and Technology https://doi.org/10.1007/s13197-025-06327-7

[11] Nikam V, Suryawanshi S, Rathod N, Kadam S. Formulation, Development and In-vitro Characterization of Modified Release Tablets of Curcumin. International Journal of Drug Delivery Technology. 2024;14(2):961-968.

[12] Hosseini, H., Ghavidel, F., Rajabian, A., Homayouni-Tabrizi, M., Majeed, M., & Sahebkar, A. (2025). The Effects of Curcumin Plus Piperine Co-administration on Inflammation and Oxidative Stress: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Current medicinal chemistry, 32(20), 4078–4094. https://doi.org/10.2174/0109298673260515240322074849

[13] Sable AA, et al. Alginate and chitosan-based delivery systems for herbal actives. J Pharm Sci. 2024;113(7):1452–1468. DOI: 10.3390/pharmaceutics16030423

[14] Arora S, et al. Piperine loaded drug delivery systems for improved biomedical applications: current status and future directions. Health Sciences Review 2023 https://doi.org/10.1016/j.hsr.2023.100138

[15] Han N, Liu Y, Liu X, Li P, Lu Y, Du S, Wu K. The controlled preparation of a carrier-free nanoparticulate formulation composed of curcumin and piperine using high-gravity technology. Pharmaceutics 2024, 16(6), 808;https://doi.org/10.3390/pharmaceutics16060808

[16] Kunnumakkara AB, et al. Role of turmeric and curcumin in prevention and treatment of chronic diseases: the evidence to date. Front Pharmacol. 2023; 14:10111629. DOI: 10.1021/acsptsci.2c00012

[17] Pratti VL, et al. Investigating bioavailability of curcumin and piperine combination: in vitro permeability and absorption study. J Pharm Biomed Anal. 2024; 217:115111. Doi: 10.2147/JEP.S427818

[18] Nugroho AK, Kusumorini N, Pramono S, Martien R. An update on nanoparticle formulation design of piperine to improve its oral bioavailability: a review. Iraqi J Pharm Sci. 2023;32(1):14-30. https://doi.org/10.31351/vol32iss1pp14-30

[19] J Yakubu, et al. Nanoparticles with curcumin and piperine modulate steroid metabolism and enhance anticancer efficacy in in vitro and in vivo models. Sci Rep. 2025; 15:98102. https://doi.org/10.1038/s41598-025-98102

[20] Tabanelli, R., Brogi, S., & Calderone, V. (2021). Improving Curcumin Bioavailability: Current Strategies and Future Perspectives. Pharmaceutics, 13(10), 1715. https://doi.org/10.3390/pharmaceutics13101715

[21] Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 4th ed. New Delhi: CBS Publishers & Distributors; 2013. (Preformulation study 217 tablet 449.)

[22] Karthika C, Hari B, Mano V, Radhakrishnan A, Janani SK, Akter R, Kaushik D, Rahman Curcumin as a great contributor for the treatment and mitigation of colorectal cancer. Experimental Gerontology. 2021 Sep 1; 152:111438. https://doi.org/10.1016/j. exger.2021.111438.

[23] Gaikwad SS, Avhad RD, Kalkotwar Formulation, development and in vitro characterization of modified release tablets of capecitabine. Drug Development and Industrial Pharmacy. 2020 Jan 2;46(1):20-30. DOI: 10.1080/03639045.2019.1698595

[24] Indian Pharmacopoeia Commission. Indian Pharmacopoeia 2022. Volumes II–III. Ghaziabad: Ministry of Health and Family Welfare, Government of India; 2022.