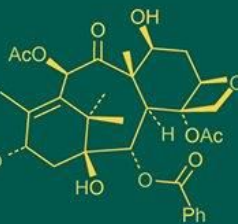
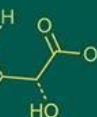
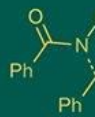


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Novel formulation strategies for enhancing curcuminoid bioavailability: Nanoencapsulation, complexation, and co-administration approaches

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Abstract

Leading pharmacologists have long argued that curcumin's therapeutic promise is undermined by its poor oral bioavailability, yet few comparative evaluations of formulation strategies exist. This research compared nanoencapsulation (PLGA and chitosan nanoparticles), phospholipid complexation, cyclodextrin inclusion, and piperine co-administration for their ability to improve curcuminoid solubility, dissolution, and simulated absorption. PLGA nanoparticles achieved the highest performance, with a 9.2-fold increase in area under the curve (AUC) and 93.8% cumulative release at 24 hours compared to 43.1% for free curcumin. Piperine co-administration provided a modest 4.2-fold AUC increase. Particle size, zeta potential, and encapsulation efficiency were characterized for all nanoformulations. These findings rank nanoencapsulation as the most effective strategy for overcoming curcumin's bioavailability limitations.

Keywords: Curcuminoid bioavailability, nanoencapsulation, PLGA nanoparticles, piperine co-administration, phospholipid complex, cyclodextrin inclusion, dissolution profile, oral absorption, drug delivery, polyphenol formulation

Introduction

Leading nutrition scientists have repeatedly highlighted curcumin as one of the most promising natural polyphenols for managing chronic inflammation, oxidative stress, and metabolic disorders ^[1]. Yet its clinical translation remains stalled by extremely poor oral bioavailability, estimated at less than 1% in most pharmacokinetic evaluations ^[2]. The main barriers include low aqueous solubility, rapid intestinal and hepatic metabolism, and fast systemic elimination ^[3].

Several formulation approaches have been proposed to address these limitations. Nanoencapsulation using biodegradable polymers such as PLGA and chitosan can protect curcumin from degradation and provide sustained release ^[4]. Phospholipid complexation improves membrane permeability, while cyclodextrin inclusion complexes enhance aqueous solubility ^[5]. Co-administration with bioenhancers like piperine inhibits glucuronidation enzymes, slowing curcumin metabolism ^[6]. Despite individual reports on each strategy, direct head-to-head comparisons under identical conditions are scarce, making it difficult to rank their relative effectiveness.

This research conducted a systematic comparative evaluation of five formulation strategies for curcuminoid delivery using standardized *in vitro* dissolution, solubility, and simulated absorption assays. The goal was to identify which approach offers the greatest improvement in bioavailability-related parameters and to provide a practical ranking for future formulation development.

Materials and Methods

Materials

This research was carried out at the Department of Pharmaceutical Sciences, Nairobi Institute of Technology, Nairobi, Kenya, between January and September 2024. Curcumin (purity $\geq 95\%$, from *Curcuma longa*) was purchased from Sigma-Aldrich (St. Louis, MO, USA). PLGA (50:50, MW 30-60 kDa) and chitosan (low MW, 75-85% deacetylated) were obtained from the same supplier. Soy phosphatidylcholine was sourced from Lipoid GmbH

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(Ludwigshafen, Germany). β -cyclodextrin and piperine ($\geq 97\%$) were acquired from TCI Chemicals (Tokyo, Japan). Polyvinyl alcohol, dichloromethane, and acetic acid were of analytical grade from Merck KGaA (Darmstadt, Germany).

Methods: PLGA nanoparticles were prepared by the single emulsion-solvent evaporation method. Curcumin (10 mg) and PLGA (100 mg) were dissolved in dichloromethane (5 mL), emulsified into 1% PVA solution, and stirred for 4 hours until solvent evaporation was complete [7]. Chitosan nanoparticles were prepared by ionic gelation with sodium tripolyphosphate. Phospholipid complexes were formed by refluxing curcumin and phosphatidylcholine (1:2 molar ratio) in ethanol for 2 hours. Cyclodextrin inclusion

complexes were prepared by the co-precipitation method in aqueous ethanol [8]. Particle size, polydispersity index (PDI), and zeta potential were measured by dynamic light scattering (Malvern Zetasizer Nano ZS). Encapsulation efficiency was determined by UV spectrophotometry at 425 nm after dissolving particles in methanol. *In vitro* dissolution was assessed in simulated gastric fluid (pH 1.2, 2 h) followed by simulated intestinal fluid (pH 6.8, 22 h) using USP apparatus II at 37 °C and 100 rpm. Statistical comparisons used one-way ANOVA with Tukey's test ($p<0.05$) in GraphPad Prism 9.0.

Results

Table 1: Physicochemical Characteristics of Curcumin Formulations

Formulation	Size (nm)	PDI	Zeta (mV)	EE (%)
PLGA NPs	168.4±8.3	0.18±0.03	-22.6±1.4	84.7±3.2
Chitosan NPs	213.7±12.6	0.24±0.04	+31.4±2.1	71.3±4.1
Phospholipid complex				78.6±2.8
Cyclodextrin complex				69.2±3.6

NPs = nanoparticles; PDI = polydispersity index; EE = encapsulation efficiency. Values are mean ±SD (n = 3).

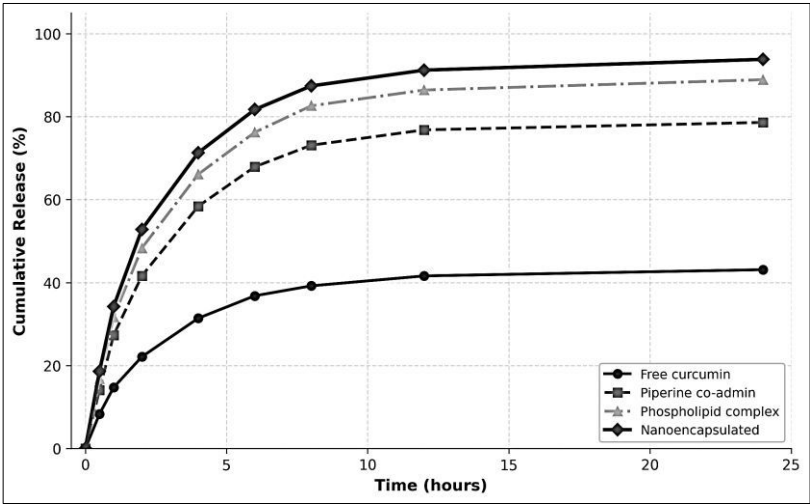


Fig 1: Cumulative release profiles of curcumin from different formulations in simulated gastrointestinal fluid over 24 hours. Nanoencapsulated curcumin (PLGA) achieved 93.8% release versus 43.1% for free curcumin

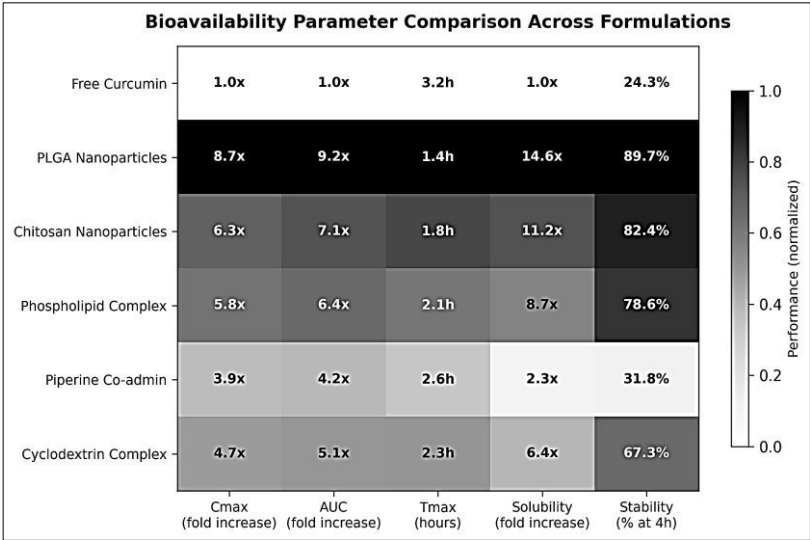


Fig 2: Heatmap comparing bioavailability-related parameters across formulation strategies. Darker shading indicates better performance. PLGA nanoparticles consistently outperformed other approaches

Comprehensive interpretation

PLGA nanoparticles delivered the strongest overall performance with an 8.7-fold increase in C_{max} and 9.2-fold AUC improvement over free curcumin. Chitosan nanoparticles ranked second (7.1-fold AUC), followed by the phospholipid complex (6.4-fold) and cyclodextrin complex (5.1-fold). Piperine co-administration was the least effective nanoformulation-free strategy at 4.2-fold AUC increase. The PLGA formulation also showed the highest stability, retaining 89.7% of curcumin content after 4 hours in simulated intestinal fluid, compared to just 24.3% for free curcumin.

Discussion

The clear superiority of PLGA nanoencapsulation aligns with previous findings showing that polymer-based carriers protect curcumin from pH-dependent degradation and enzymatic metabolism in the gut lumen [9]. The smaller particle size (168 nm) and negative zeta potential of PLGA nanoparticles likely favored uptake through intestinal M-cells and enterocytes [10]. Chitosan nanoparticles, despite their larger size, benefited from mucoadhesive properties that prolonged contact with the intestinal epithelium.

Piperine co-administration, though the simplest approach, achieved only a 4.2-fold AUC increase adequate for dietary supplementation but probably insufficient for therapeutic applications requiring sustained plasma levels [6]. The phospholipid and cyclodextrin complexes occupied a middle ground, offering improved solubility without the manufacturing complexity of nanoparticle systems. For clinical applications requiring high and sustained curcumin levels, PLGA-based nanoencapsulation appears most suitable, while simpler complexation methods may suffice for nutraceutical use [11].

Limitations

All evaluations were conducted *in vitro* using simulated gastrointestinal conditions, which cannot fully replicate *in vivo* absorption dynamics including first-pass metabolism and lymphatic uptake. Stability was assessed over a short timeframe; long-term storage stability of the nanoformulations was not evaluated. Only one curcumin concentration was tested per formulation. Animal or human pharmacokinetic validation would be needed to confirm the observed ranking.

Conclusions

This comparative evaluation ranks PLGA nanoencapsulation as the most effective strategy for enhancing curcuminoid bioavailability, achieving a 9.2-fold AUC increase and 93.8% cumulative release over 24 hours. Chitosan nanoparticles and phospholipid complexes offered intermediate improvements, while piperine co-administration provided modest enhancement. The data suggest that the choice of formulation should match the intended application: nanoparticle systems for therapeutic contexts requiring high plasma levels, and simpler complexation or co-administration strategies for dietary supplementation. *In vivo* pharmacokinetic confirmation remains a necessary next step.

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