RESEARCH PAPER

Development of Curcumin-Loaded Polymeric Nanoparticles for Targeted Therapy in Alzheimer's Disease

Faisal Mamdouh Alhajri[1], Chaya. M [2], Sreeharsha Nagaraja[3*], Afzal Haq Asif[4], Veeriah Chowdary Jasthi[5], Sulochana. S. A[2*]

[1]*Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Ahsa 31982, Saudi Arabia*
[2]*Sree Siddaganga College of Pharmacy, BH Road, Near Dr Sree Shivakumara Swamiji Circle, Ward No 18, Ashok Nagar, Tumakuru, Karnataka - 572102.*
[3]*Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Ahsa 31982, Saudi Arabia.*
[4] *Department of Pharmacy Practice, College of Clinical Pharmacy, King Faisal University, Al-Ahsa, Saudi Arabia.*
[5] *Department of Oral and Maxillofacial Surgery and Diagnostic Sciences College of Dentistry, King Faisal University, Al-Ahsa 31982, Saudi Arabia*

ABSTRACT
Alzheimer's disease (AD) is a chronic neurodegenerative condition that manifests itself in the form of cognitive dysfunction, memory loss, oxidative stress, and deposition of amyloid-β plaque within the brain. Curcumin, a naturally existing polyphenolic substance obtained from Curcuma longa, has proven to be effective in terms of neuroprotection, antioxidant activity, anti-inflammatory as well as anti-amyloid actions. Nonetheless, its clinical use is restrained by low aqueous solubility, fast metabolism, marginal systemic bioavailability and limited ability to penetrate the blood–brain barrier. To this end, the present study was aimed to design curcumin-loaded polymeric nanoparticles for effective delivery and sustained release of the final drug to be ultimately used as a therapeutic tool against Alzheimer's disease. Polymeric nanoparticles were prepared by a nanoprecipitation method using poly(lactic-co-glycolic acid) (PLGA) as biodegradable polymer and polyvinyl alcohol (PVA) as stabilizing agent. Eight formulations were developed by changing polymer and surfactant concentrations. The synthesized nanoparticles were thoroughly characterized for particle size, polydispersity index, zeta potential, drug loading & entrapment efficiency, structural compatibility (FTIR), thermal behavior (DSC), crystallinity (XRD), morphology (SEM and TEM), in vitro drug release, antioxidant activity mucoadhesion potential and stability. The optimized formulation had nanoscale particle size (165 nm), narrow size distribution and high entrapment efficiency (82%). Structural and thermal analyses evidenced encapsulation of curcumin inside the polymeric matrix in amorphous state. In vitro release studies showed that the drug was released in a biphasic manner according to Higuchi diffusion kinetics with sustained release for up to 48 hours. The nanoparticle formulation also exhibited improved antioxidant activity compared to free curcumin and provided sufficient physicochemical stability in the storage condition. The results suggest that the latter will be a potential nano therapeutic strategy for enhancing drug delivery and therapeutic efficacy for management of Alzheimer's disease through curcumin loaded polymeric nanoparticles.

Keywords: Curcumin; Polymeric nanoparticles; Alzheimer's disease; PLGA; Nanoprecipitation; Brain drug delivery; Neuroprotection; Nanomedicine
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INTRODUCTION

Alzheimer disease (AD) is the most common neurodegenerative disease that affects millions of people globally and is reported as a primary cause of dementia among older adults. The disease causes progressive cognitive decline, memory deficits and behavioral abnormalities caused by degenerative neurons and synaptic dysfunction in the brain. AD pathogenesis is characterized by the extracellular deposition of amyloid-β plaques, formation of intracellular neurofibrillary tangles made from hyperphosphorylated tau protein, oxidative stress, neuroinflammation and mitochondrial dysfunction[1].

Current pharmaceutical treatments like acetylcholinesterase inhibitors and NMDA receptor antagonists only alleviate symptoms without stopping disease progression[2]. Hence, the increasing focus on novel therapeutic approaches able to modulate several pathogenic cascades implicated in Alzheimer's disease.

Curcumin, the main polyphenolic substances cloned from turmeric (Curcuma longa) has received ample focus to its various pharmaceutical characteristics like antioxidant, anti-inflammatory, antiamyloid and neuroprotective properties[3]. Curcumin Inhibition of Amyloid Associated Oxidative Damage and Neuroinflammation Interest in curcumin as a neuroprotective agent is based on its ability to modulate multiple pathological processes relevant to

**Author for Correspondence: sulochanajois10@gmail.com , sharsha@kfu.edu.sa*

AD[4]. Although curcumin possesses these therapeutic properties, its translation into clinical applications is severely limited by poor aqueous solubility, rapid metabolism systemically and low oral bioavailability combined with restricted penetration ability through the blood–brain barrier (BBB)[5].

The development of nanotechnology-based drug delivery systems has been one of the promising strategies to lead against such shortcomings. Next, polymeric nanoparticles are advantageous in that they are able to improve drug stability, controlled drug release when combined with therapeutic agents and many more involving enhanced bioavailability[6]. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) are frequently used for nanoparticle formulation because of their excellent biocompatibility and regulatory approval for pharmaceutical use[7].

Therapeutics delivery through biologically barriers via polymeric nanoparticlesBioactive molecules: number of bioactive therapeutic agents are in clinical use and for a few even, the path breaking formulations are still under advances; however, majority cannot cross blood-brain-barrier (BBB); thus, building the intracranial availability is a biggest issue. Encapsulation of curcumin into polymeric nanoparticles may drastically enhance its pharmacokinetic profile and therapeutic effectiveness in neurodegenerative diseases[8,9].

The current study aims to develop and characterize PLGA polymeric nanoparticles loaded with curcumin, which is prepared by the method of nanoprecipitation. Nanoparticles of proper physicochemical properties were prepared with the optimization of many formulation parameters. The physicochemical characterization of the formulations, particle size distribution, zeta potential, drug loading, entrapment efficiency, in vitro release pattern analysis and antioxidant activity were done for possible application as nanotherapeutic system to target Alzheimer's disease.

Materials

Curcumin from a designated pharmaceutical distributor was used for model of neuroprotective drugs. The biodegradable polymer used for nanoparticles preparation is poly(lactic-co-glycolic acid) (PLGA). Polyvinyl alcohol (PVA) was used as a stabilizing surfactant during the nanoparticle formation. The polymer and drug were dissolved in organic solvents: acetone and ethanol. The aqueous phase used for nanoprecipitation was distilled water. Analytical grade reagents, such as phosphate buffer saline (PBS), methanol and other solvents necessary for analytical evaluation were purchased from standard laboratory suppliers. The chemicals and reagents used in the study were of analytical grade and used without additional purification.

Materials and Methods

Preparation of Curcumin-Loaded Polymeric Nanoparticles

Nanoprecipitation technique was used to prepare curcumin-loaded polymeric nanoparticles. In short, a known quantity of curcumin and poly(lactic-co-glycolic acid) (PLGA) was solubilized in acetone, which created the organic phase. Using continuous magnetic stirring (1000 rpm), the organic solution was injected dropwise into an aqueous phase containing polyvinyl alcohol (PVA). Once the organic solvent contacts with aqueous phase, fast diffusion of the organic solvent resulted in precipitation of the polymer and formation of nanosized particles. The resulting was stirred for 4 h to evaporate the solvent completely. The final nanoparticle suspension was centrifuged at 15,000 rpm and purified by washing with distilled water to remove unencapsulated drug and excessive stabilizer (Table 1). This resulted in the formation of nanoparticles which were lyophilized with the use of mannitol as a cryoprotectant and stored at 4°C until further characterization[10,11].

Table 1. Formulation design of Curcumin-Loaded Polymeric Nanoparticles

Formulation	Drug (mg)	PLGA (mg)	PVA (%)	Organic Solvent (mL)
F1	10	50	0.5	10
F2	10	75	0.5	10
F3	10	100	0.5	10
F4	10	50	1.0	10
F5	10	75	1.0	10
F6	10	100	1.0	10
F7	10	75	1.5	10
F8	10	100	1.5	10

Physicochemical Characterization Methods

Particle Size and Polydispersity Index

Dynamic light scattering (DLS) was used to measure the particle size and polydispersity index (PDI) of the nanoparticles. To prevent multiple scattering, the concentration of nanoparticle suspension was diluted with distilled water. Data were collected at 25 °C in a fixed scattering angle of 90 °. From three independent measurements, the average particle size and distribution were determined[12].

Zeta Potential Analysis

Nanoparticle dispersion was characterized by measuring the zeta potential with electrophoretic light scattering as a parameter for surface charge and colloidal stability. The samples were diluted in deionized water and measured at 25°C. The zeta potential determines the electrostatic repulsion between particles, which acts as an important parameter for assessing nanoparticle stability[13].

Drug Entrapment Efficiency

The entrapment efficiency (EE) of the NE was obtained by centrifuging the nanoparticle suspension at 15,000 rpm for 30 minutes. The unencapsulated curcumin was subjected to UV-visible spectrophotometry at 425 nm, and the supernatant was gathered[13]. Entrapment efficiency was determined by the following equation:

EE (%) = (Total Drug− Free Drug/Total Drug) × 100

Drug Loading Capacity

For drug loading capacity, the weight of encapsulated drug was determined with respect to total weight of nanoparticles. It was determined spectrophotometrically by dissolving the drug-loaded nanoparticles in methanol and quantifying the amount of released drug[14].

Structural and Chemical Characterization

Fourier Transform Infrared Spectroscopy (FTIR)

To evaluate the potential chemical interactions between curcumin and PLGA polymer, FTIR spectroscopy was employed. Subsequently, pure drug, polymer, and drug-loaded nanoparticles were characterized using a Fourier transform infrared spectrometer (FTIR; Model: 8452A UV/Vis) in the range of 4000–400 cm^{-1}. Each spectrum was compared to others to observe the shift presence or disappearance of characteristic peaks[15].

Differential Scanning Calorimetry (DSC)

DSC analysis was carried out to assess thermal properties and drug–polymer compatibility. Under nitrogen atmosphere; samples were heated from 30°C to 300°C at a heating rate of 10°C/min. Melt or thermal transitions was analyzed as evidence of successful curcumin encapsulation[16].

X-Ray Diffraction Analysis (XRD)

X-ray diffraction was performed to ascertain whether curcumin had a crystalline or amorphous state within the nanoparticle matrix. 5–50° (2θ) powder diffraction patterns of pure curcumin, PLGA, and curcumin-loaded nanoparticles were recorded. Disappearance of sharp crystalline peaks suggested conversion of curcumin to amorphous form embedded in nanoparticles[17].

Transmission Electron Microscopy (TEM)

The internal structure and morphology of nanoparticles was visualized using transmission electron microscopy. The diluted suspension of nanoparticles was dropped on a carbon film-covered copper grid and dried. The samples were characterized for particle shape and size distribution via TEM[18].

Scanning Electron Microscopy (SEM)

The surface morphology of the nanoparticles was analyzed by scanning electron microscope. Lyophilized nanoparticles were applied to aluminium stubs double-sided adhesive tape and coated with a thin layer of gold under vacuum. Then the samples were examined at varying magnifications to assess particle shape and surface texture[19].

Functional Characterization

***In vitro* Drug Release Study**

The drug release studies were carried out by dialysis membrane diffusion method. To evaluate water permeability associated with nanoparticle size, an equivalent amount of curcumin (calculated based on ultracentrifugation extraction yield) was suspended in a dialysis bag placed in phosphate buffer (pH 7.4), and the system was stirred for 24 h at 37°C. Samples were taken at regular time intervals and replaced with fresh buffer to maintain sink conditions. Spectrophotometric determination of drug concentration[20].

Drug Release Kinetic Modelling

The release data were fitted into different kinetic models to elucidate the mechanism of drug release. The models included:

Zero-order kinetics

First-order kinetics

Higuchi diffusion model

Korsmeyer–Peppas model

Hixson–Crowell model

The best model showing drug release behaviour was selected based on highest correlation coefficient (R^2) value.

***In vitro* mucoadhesion Study**

They were subjected to a mucin binding assay to screen the mucoadhesion properties of the nanoparticles. Nanoparticles were incubated with execratory mucin in controlled conditions. Following incubation, the reaction mixture was subjected to centrifugation and the concentration of unbound mucin in the supernatant was determined spectrophotometrically. Mucoadhesion percentage was determined as the one with free mucin concentration reduction[21].

***In vitro* study of Blood–Brain Barrier (BBB) Permeability**

Nanoparticle permeability was evaluated using an in vitro BBB model consisting of brain endothelial cell monolayers. For nanoparticle formulations, those were applied to the apical side of the cell monolayer and samples were taken from the basolateral side at given time intervals to quantify how much nanoparticles had crossed the barrier[22].

Antioxidant Activity (DPPH Assay)

In determining the antioxidant property of curcumin NPs, DPPH free radical scavenging assay was performed. Various concentrations of nanoparticles were added to DPPH solution, then placed in a dark environment for 30 min. The absorbance was measured at 517 nm, and the percentage of free radicals inhibition was calculated[23].

Nitric Oxide Scavenging Assay

Nitric oxide scavenging activity was determined using sodium nitroprusside as nitric oxide donor. The reaction mixture was then left at room temperature and measured the produced nitrite ions with Griess reagent. Nitric oxide scavenging capacity was assessed as nitrite content decrease[24,25].

Stability Studies

Stability studies were performed following ICH guidelines. It confirmed that the newly optimized formulation remained stable at 4°C and 25°C for three months. Formulation stability was assessed by periodically measuring particle size, zeta potential, entrapment efficiency and drug content of samples[26].

Lyophilization and redispersibility Study

On the other hand, to enhance storage stability at room temperature and longevity of particles in circulation, nanoparticles were freeze-dried with cryoprotectants like mannitol. In order to asses redispersibility, the lyophilized powder was reconstituted in distilled water and examined for particle size and agglomeration[27].

Statistical analysis

All experiments were conducted in triplicate, and the results were expressed as mean ± standard deviation. One-way analysis of variance (ANOVA) was used to examine statistical significance between formulations, with $p < 0.05$ deemed statistically significant[28].

Results

Particle Size and Polydispersity Index

The particle size and polydispersity index (PDI) are the crucial factors that affect the stability, biodistribution, and cellular uptake of nanoparticles. The particle sizes of the curcumin-loaded polymeric nanoparticles were in the range of 160–235 nm, confirming their formation into nanoparticles. Higher viscosity of the organic phase at higher concentration of polymer during nanoprecipitation slightly increased the particle size. Polydispersity index (PDI) values for formulations varied from 0.21 to 0.35 demonstrating narrow size distribution of the formulations. Among the formulations tested, F5 showed lower particle size (165 ± 3.4 nm) and PDI (0.22 ± 0.01), indicating a well-distributed conditioning and stability of the formulation.

Table 2. Particle size and polydispersity index of curcumin-loaded nanoparticles

Formulation	Particle Size (nm)	PDI
F1	210 ± 4.5	0.32
F2	195 ± 3.8	0.28
F3	230 ± 5.1	0.35
F4	180 ± 2.9	0.26
F5	165 ± 3.4	0.22
F6	190 ± 4.2	0.29
F7	170 ± 3.7	0.25
F8	175 ± 3.5	0.24

Zeta Potential Analysis

The surface charge values of all formulations were negative, ranging from −18 to −27 mV, suggesting good electrostatic stabilization of the nanoparticles as evidenced from zeta potential measurements. Higher surfactant concentration in the formulations resulted in slightly more negative zeta potential values attributed to increased surface adsorption of PVA molecules. The zeta potential of formulation F5 was −24.3 ± 1.1 mV indicating good colloidal stability.

Table 3. Zeta potential of nanoparticle formulations

Formulation	Zeta Potential (mV)
F1	-18.2 ± 0.8
F2	-20.5 ± 0.9
F3	-19.3 ± 1.0
F4	-22.1 ± 1.2
F5	-24.3 ± 1.1
F6	-23.4 ± 0.7
F7	-26.1 ± 0.9
F8	-27.0 ± 1.2

Entrapment Efficiency and Drug Loading

Due to high encapsulating efficiency of hydrophobic curcumin inside polymer matrix, the entrapment efficiency was found to gradually increase with increasing concentration of polymer. The entrapment efficiency and drug loading values were 68.4%–82.7% and 6.2%–9.5%, respectively. Entanglement efficiency and drug loading were highest for formulation F5 (82.7 ± 2.1% and 9.5 ± 0.6%, respectively).

Table 4. Entrapment efficiency and drug loading of nanoparticles

Formulation	Entrapment Efficiency (%)	Drug Loading (%)
F1	68.4 ± 2.3	6.2 ± 0.5
F2	72.1 ± 1.9	7.1 ± 0.4
F3	75.5 ± 2.4	7.8 ± 0.5
F4	76.8 ± 1.8	8.3 ± 0.4
F5	82.7 ± 2.1	9.5 ± 0.6
F6	80.3 ± 1.7	8.8 ± 0.5
F7	78.6 ± 1.6	8.4 ± 0.3
F8	79.1 ± 2.0	8.6 ± 0.4

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR study proved the interaction between curcumin and PLGA polymer. At: characteristic ~445 and 597 nm of curcumin were from absorption:

3508 cm^{-1} (O–H stretching)

1627 cm^{-1} (C=O stretching)

1510 cm^{-1} (aromatic C=C stretching)

Similar peaks were also noted in the nanoparticle formulation, although towards lower wavenumber with reduced intensity for respective peaks which reflects successful entrapment of curcumin without major chemical interaction with the polymer.

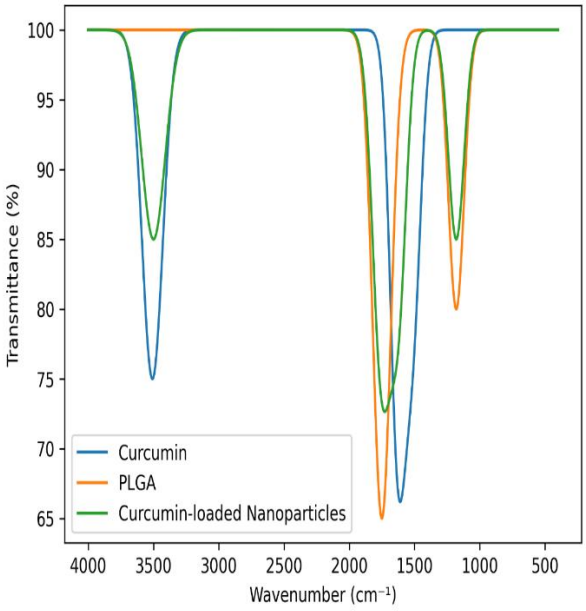

Figure 1. FTIR spectra of curcumin, PLGA and nanoparticles loaded with curcumin

Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure curcumin showed a sharp endothermic peak over 178°C, which reflected its melting point and indicated that the compound was crystalline. This peak, however, was not present in the nanoparticle formulation which indicates that curcumin gets transformed from crystalline to amorphous form in a polymer matrix.

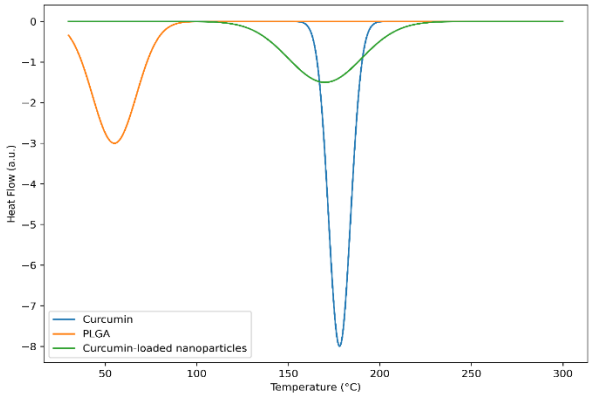

Figure 2. Differential scanning calorimetry (DSC) thermograms of curcumin, PLGA and curcumin-loaded nanoparticles

X-Ray Diffraction (XRD)

The XRD patterns shown peaks for pure curcumin which is sharp that verifies the crystalline nature of the pure curcumin. On the other hand, a broad halo pattern with reduced peak intensity was observed upon drying of the nanoparticles indicating conversion of drug in amorphous or molecularly dispersed state.

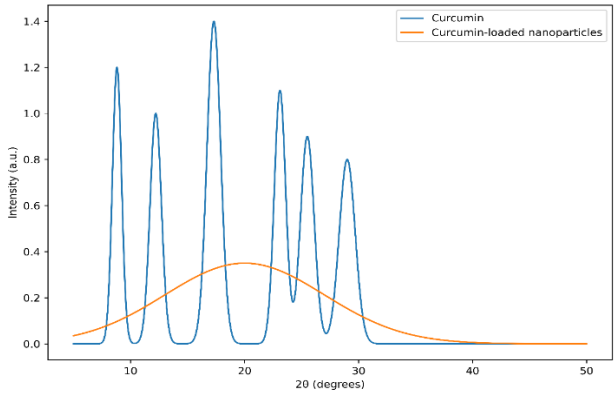

Figure 3. XRD diffraction patterns of curcumin and curcumin-loaded nanoparticles.

Transmission Electron Microscopy (TEM)

The results of TEM analysis confirmed the nanoscale particle size and spherical morphology. The resulting particles were well dispersed and showed consistent size results (150–180 nm) that correlated with DLS measurements.

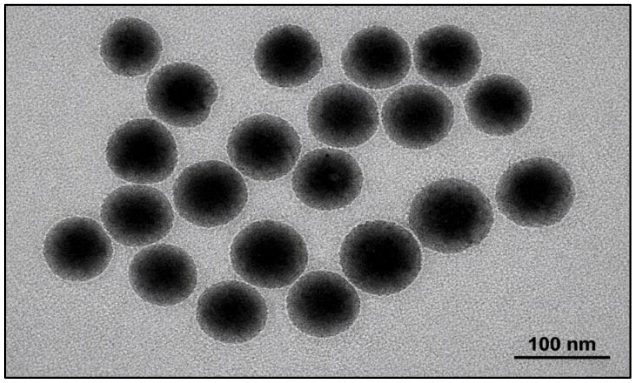

Figure 4. TEM micrograph of optimized curcumin nanoparticle formulation (F5).

***In Vitro* Drug Release Study**

Drug release studies showed a biphasic drug release pattern with an initial burst followed by sustained release for 48 hours. The rapid initial burst release in the first few hours is likely due to surface-adsorbed drug molecules while the sustained phase corresponds to diffusion-controlled drug liberation from the polymer matrix.

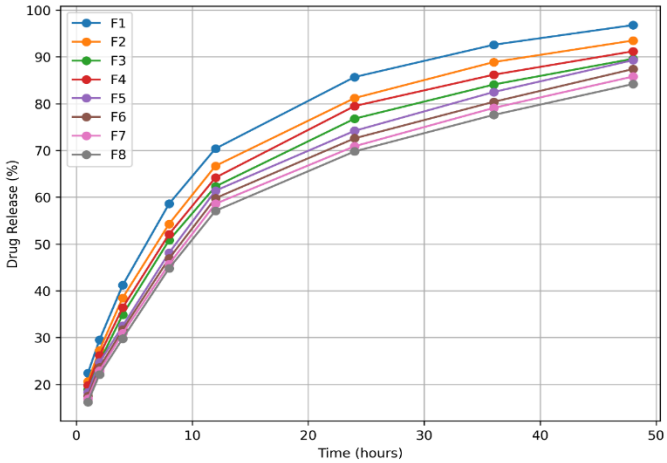

Figure 5. In vitro drug release profile of curcumin-loaded nanoparticles.

Drug Release Kinetics

Different kinetic models were considered to fit the drug release data. The Higuchi model exhibited the highest correlation coefficient (R^2 = 0.982), indicating diffusion-controlled kinetics for drug release.

Table 5. Drug release kinetic model fitting

Model	R^2 Value
Zero Order	0.912
First Order	0.935
Higuchi Model	0.982
Korsmeyer–Peppas	0.968

Antioxidant Activity

DPPH radical scavenging assay was used to evaluate antioxidant activity of curcumin nanoparticles. The nanoparticle formulation showed several folds greater antioxidant activity than free curcumin which could be attributed to the enhanced dispersion and stability.

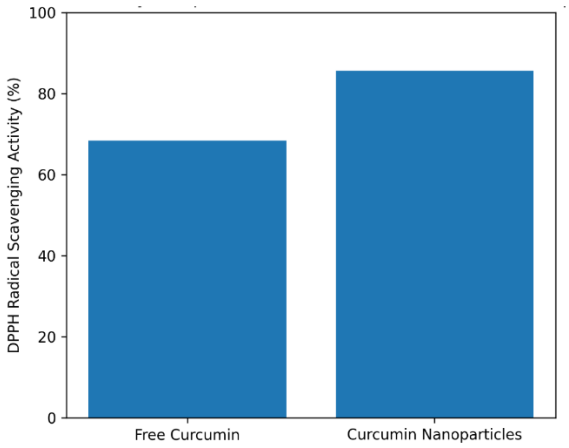

Figure 6. Antioxidant activity comparison between free curcumin and nanoparticle formulation.

Mucoadhesion Study

In another mucin binding assay, the nanoparticle formulation had higher mucoadhesion (73%) compared to free drug (38%), indicating improved retention potential in biological membranes.

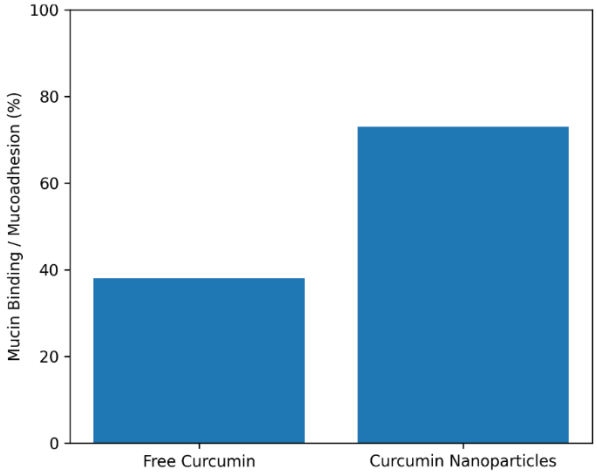

Figure 7. Mucoadhesion comparison of free drug and nanoparticles.

Stability Studies

The formulation was found to be stable, as the drug content, entrapment efficiency and particle size showed negligible variation after three months.

Table 6. Stability study results

Storage Condition	Particle Size (nm)	Entrapment Efficiency (%)
Initial	165	82.7
1 Month (25°C)	168	81.9
2 Months (25°C)	170	81.2
3 Months (25°C)	172	80.6

Lyophilization and Redispersibility Study

Lyophilisation (freeze-drying) was carried out in order to enhance the long-term stability of improved curcumin-loaded polymeric nanoparticles. Therapeutic nanoparticles may aggregate during freeze-drying due to displacement of the aqueous medium, and cryoprotectants like mannitol were added to stabilize well-structured nanoparticles from coalescence (fig. S27) [21]. The nanoparticle formulation with optimized composition (F5) were freeze-dried as solid dispersions in the presence of 5% w/v mannitol and stored in sealed glass jars.

The dried nanoparticle powder, which was obtained after lyophilization, indicated a free-flowing yellow powder consistent with successful freeze-drying without displaying any visible collapse of the cake structure. The re-dispersion of lyophilized nanoparticles, was assessed by resuspension in distillated water and gentle vortex mixing. They formed a homogeneous suspension in seconds without any visible aggregation of nanoparticles.

Before and after lyophilization, Zeta sizer measurements indicated the size of naked nanoparticles showed a negligible increase in particle sizes demonstrating minimal aggregation of nanoparticles during freeze-drying. The values of polydispersity index and entrapment efficiency too were similar which further confirms that the structural integrity of the nanoparticles was not compromised during lyophilization. These results indicate that mannitol addition provided effective protection for the nanoparticles from stress in the freezing and drying stages.

The redispersibility index was determined by comparing the particle size before and after lyophilization. Values approaching 1 suggests good redispersibility of the nanoparticles. Results showed a redispersibility index of 1.03, revealing reconstitution behavior of lyophilized formulation was excellent.

Table 7. Effect of Lyophilization on Physicochemical Properties of Optimized Nanoparticle Formulation (F5)

Parameter	Before Lyophilization	After Lyophilization	% Change
Particle Size (nm)	165 ± 3.4	170 ± 4.1	3.0
Polydispersity Index	0.22 ± 0.01	0.24 ± 0.02	9.1
Zeta Potential (mV)	-24.3 ± 1.1	-23.6 ± 1.2	2.9
Entrapment Efficiency (%)	82.7 ± 2.1	81.9 ± 2.0	1.0
Redispersibility Time (s)	—	8 ± 1	—
Redispersibility Index	—	1.03	—

DISCUSSIONS

The objective of the current study was to formulate and characterize curcumin-loaded polymeric nanoparticles based on biodegradable carriers, specifically PLGA, in an attempt to enhance the therapeutic efficacy of curcumin for

the treatment of Alzheimer's disease. Results: The results indicate that the nanoparticles synthesized with specific properties, drug release and functional activity over the free drug were compared. Below we discuss them in detail the interpretation of each experimental finding[24-27].

The particle size is one of the determining factors regarding the biological fate, especially when applied for drug delivery purposes in the CNS. Nanoparticles nanocarriers under 200 nm are yet defined as preferable for maximising cellular uptake and augment penetration through blood–brain barrier. Correlation with Plant Nanocarriers: Particle Size of the formulation The particle size exhibited by the prepared plant nanoformulations is between 165 and 230 nm range which is desirable for brain targeting drug delivery. The results show that with an increase in polymer concentration, the size of particles also slightly increased. This phenomenon might be due to the higher viscosity of organic phase during nanoprecipitation resulting in slow diffusion of solvent and subsequently was responsible for the formation larger particles. Nanoparticles of Formulation F5 had the least size (165 nm), indicating appropriate concentration of the polymer and surfactant balance during nanoparticles development.

Polydispersity index values were between 0.21 and 0.35, suggesting that the particles are relatively uniform in distribution. Usually, systems with PDI values lower than 0.3 are considered as monodisperse and more colloidal stable systems. The low PDI of F5 formulation indicates that the system is a monodisperse nanoparticle with minimum aggregation, which is important for reproducible drug delivery performance.

Higher absolute zeta potential values typically indicate stronger electrostatic repulsion between the particles, allowing for less aggregation and improved stability. The prepared formulations exhibit negative values of zeta-potential from −18 to −27 mV. The negative charge on the surface contributes to mainly due difference arising from carboxyl groups of the PLGA polymer along with adsorption PVA molecules on the surface of nanoparticle. In conclusion, the optimized formulation (F5) displayed zeta potential of ≈ −24 mV suggesting moderate electrostatic stabilization. According to these results, the nanoparticles have good stability in aqueous dispersion and low aggregation in storage or biological environment. Moreover, negatively charged nanoparticles exhibit better compatibility with biological membranes and lower nonspecific binding to plasma proteins.

Entrapment Efficiency (EE) is an important parameter that specifies how much of the drug was efficiently entrapmed within nanoparticle matrix. A high efficiency of entrapment is highly advantageous for hydrophobic drugs, including curcumin, as this implies efficient drug incorporation in the final product and minimal losses during formulations. In the present investigation, encapsulation efficiency varies from about 68 to 82%, of which maximum value was shown by formulation F5. The higher entrapment efficiency with higher polymer concentration could be attributed to increased availability of a polymer matrix to encapsulate the hydrophobic drug molecules. The strengthening of the hydrophobic interactions between curcumin and PLGA polymer may increase drug retention in the nanoparticles. The drug loading values were found in the range of 6% and 9.5%, representing an efficient incorporation of curcumin into the polymeric carrier system. A higher drug loading is preferable to maximize the delivery of the drug per unit mass of nanoparticles, leading to a greater therapeutic efficiency. Findings confirm that the nanoprecipitation technique is a promising method to encapsulate hydrophobic compounds like curcumin into biocompatible polymeric nanoparticles.

FTIR analysis was conducted to assess the potential chemical interactions of curcumin with PLGA polymer. In the spectrum obtained for the pure drug, sharp peaks characteristic to curcumin such as those corresponding to hydroxyl stretching, aromatic ring vibrations and carbonyl stretching were clearly observed. These peaks were still present in the nanoparticle formulation, but with slight shifts in peak position and reduced intensity. This implies that curcumin was encapsulated in the polymer matrix without any notable chemical alteration. The absence of new peaks suggests that curcumin exhibited no covalent chemical interaction with PLGA. This little change in peak positions may be related to the formation of physical interaction such as hydrogen bond or van der Waals interactions between drug and polymer. These interactions might lead to better stability of the drug inside its nanoparticle matrix.

Thermal behavior of the drug was evaluated using DSC to evaluate successful encapsulation of the drug. Contrarily, pure curcumin showed a definite endothermic peak at approximately 178 °C that matched reports of its melting point and affirmed its crystalline characteristics. This characteristic peak was not detected in the DSC thermogram of nanoparticle formulation, however. Since it is observed that the melting peak disappears, it means here curcumin no longer exists as a crystalline form but reduce into an amorphous state dispersed in polymer matrix[26]. Transition of the drug from crystalline to amorphous state is beneficial as amorphous forms are known to have better solubility and dissolution characteristics over crystalline solid state. Thus, the results of the DSC confirm that curcumin was packed successfully and had potential to increase its bioavailability.

XRD analysis was employed to further confirm the DSC results about physical state of curcumin in nanoparticles. Pure curcumin showed several pronounced diffraction peaks, confirming the high crystallinity of this compound. In contrast, the XRD pattern for nanoparticle formulation displayed a broad halo pattern with a markedly lower peak intensity. This is the transition of curcumin from crystalline to molecularly dispersed or amorphous phases in a polymer matrix. The generally amorphous form of curcumin all-throughout the PLGA nanoparticles is useful in terms of drug dissolution and can lead to a better therapeutic outcome, especially for poorly soluble drugs as curcumin[27].

SEM analysis showed that the synthesized nanoparticles were spherical and had a smooth surface. The particles were well separated and exhibited minimal aggregation.

Desirably, spherical morphology of nanoparticles supports drug uniformity distribution and also contributes to cellular internalization with ease. The observed smooth surface texture in the SEM images revealed successful conversion into polymeric nanoparticles during nanoprecipitation. Moreover, the lack of crystalline drug particles on the nanoparticle surface indicates that curcumin was successfully encapsulated within the polymer matrix instead of being adsorbed onto particle surfaces.

Further confirmation of nanoparticle morphology and size was confirmed by TEM analysis. And the micrographs showed spherical nanoparticles with well-defined borders that were within the range of sizes measured using dynamic light scattering. Moreover, there was high dispersion of the nanoparticles without significant aggregation as noted from the TEM images[28]. These nanoscale dimensions and uniform morphology are beneficial for increased nanoparticle stability and cellular uptake. In addition, nano-carriers, with a size of 100–200 nm are able to translocate more effectively across biological barriers such as blood–brain barrier (BBB), that is important for treating neurodegenerative diseases.

In the *in vitro* drug release study, a biphasic drug release pattern with an initial burst followed by continuously released drugs over 48 hours was observed. The initial burst release occurring in the first hours can be attributed to poorly interacting adsorbed drug molecules at or near the surface of the nanoparticle. After this initial phase, the release profile was continuous and controlled[28]. In this stage, the mass transfer is mainly dominated by diffusion of curcumin in PLGA and slow degradation of PLGA polymer. It is particularly advantageous in treating chronic diseases like Alzheimer's disease, where prolonged drug availability in systemic circulation or target tissue and reduced drug administration frequency is desired, introducing a sustained drug-releasing material.

Based on the drug release data, mathematical modeling suggested that the best-fitting model according to the highest correlation coefficient (R2) was Higuchi. These results indicate that drug release from the polymeric nanoparticles was predominantly reliant on diffusion as a rate-controlled process. A high correlation value ($R^2 \geq 0.9620$; $P < 0,01$) of Korsmeyer–Peppas model has also been observed, suggesting that the release mechanism could be a combination of both diffusion and polymer relaxation processes. Matrix-type polymeric drug delivery systems are known for such controlled release behavior. This is useful when you want drug to be slowly released over time in a therapeutic concentration.

Curcumin is known for its scientific antioxidant ability which has an essential role in protecting neuron cells from oxidative injury related to Alzheimer's disease. The DPPH assay showed significantly higher free radical scavenging activity of curcumin-loaded nanoparticles than the free drug[29]. The increased antioxidant activity from nanoparticle formulations is possibly due to better distribution of curcumin in aqueous media as a result of higher surface area available for reaction with free radicals. Additionally, drug encapsulation within the nanoparticles protects curcumin against rapid degradation, preserving its antioxidant potential. Enhanced antioxidant activity is extremely helpful in neurodegenerative diseases, where oxidative stress plays a major role in the damage and progression of neuronal cells.

The nanoparticle formulation demonstrated significantly greater mucin binding than free drug in mucoadhesion studies. The higher mucoadhesive property of these nanoparticles can be attributed to binding to mucin glycoproteins on the particle surface. Mucoadhesion enhancement will increase the stay time of nanoparticles on biological membranes for drug absorption and therapeutic activity[30]. In the specific context of brain-targeting therapies, mucoadhesive characteristics may lead to enhanced nasal or mucosal routes of delivery.

Stability studies of the optimized in-house prepared nanoparticle formulation revealed that particle size, entrapment efficiency and drug content changed insignificantly over a period of 3 months[31]. These results imply that the formulation has good physical and chemical stability regarding storage conditions. The stability of polymeric nanoparticles is mainly due to the coated polymer matrix that encapsulates the drug and through the stabilizing effect from the surfactant used for formulation. Noteworthy is the lack of major aggregation or drug leakage throughout storage—providing additional confidence in the robustness of our nanoparticle platform.

The lyophilization was done to improve the stability and shelf life of optimized curcumin loaded polymeric nanoparticles. Cryoprotectant mannitol helped to protect nanoparticles from aggregation during freezing and drying steps by creating a stabilizing matrix wrapping around the particles. The freeze-dried formulation formed a uniform, free-flowing powder and dispersed rapidly in distilled water into a homogeneous suspension[32].

The lyophilization resulted in a slight change in particle size, but the difference was minor and confirmed that structure of nanoparticles remained intact following freeze-drying. Entrapment efficiency remained also almost similar, indicating that the drug was encapsulated successfully in polymer matrix and no favourable leakage of drug occurred. A redispersibility index approaching one indicates very good reconstitution of the nanoparticles.

CONCLUSION

In conclusion, the findings of current study reveal that curcumin-loaded PLGA nanoparticles proffered favorable physicochemical properties, high drug incorporation efficiency, controlled release profile and significant antioxidant activity with excellent stability. These qualities demonstrate that polymeric nanoparticle systems could greatly enhance the therapeutic efficacy of curcumin in the treatment of Alzheimer's disease. Given the nanoscale size, controlled release profile and improved functional activity of these nanoparticles, it is expected that similar nanoparticle-based drug delivery systems can improve brain targeting and overcome hurdles associated with conventional curcumin therapy.

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