Redox-Responsive Curcumin-Loaded Polymeric Nanoparticles for Targeted Therapy of Parkinson's Disease-Associated Neuroinflammation

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss, oxidative stress, and chronic neuroinflammation. The present study focuses on the development of redox-responsive curcumin-loaded polymeric nanoparticles as a targeted therapeutic strategy for PD-associated neuroinflammation. Curcumin was encapsulated within biodegradable PLGA/PEG-based nanoparticles incorporating disulfide linkages to enable reactive oxygen species (ROS)-triggered drug release. The formulated nanoparticles were evaluated for physicochemical properties, in vitro drug release behavior, cellular uptake, cytotoxicity, anti-inflammatory activity, oxidative stress modulation, and in vivo neuroprotective efficacy. The nanoparticles exhibited uniform nanoscale size distribution, high encapsulation efficiency, and stable surface charge, indicating suitability for brain-targeted delivery. In vitro studies demonstrated controlled drug release under physiological conditions and significantly enhanced release under oxidative environments, confirming redox responsiveness. Cellular studies in microglial and neuronal models showed improved uptake, minimal cytotoxicity, and significant reduction in ROS levels and apoptosis. Anti-inflammatory assays revealed suppression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and inhibition of microglial activation. Furthermore, oxidative stress markers were significantly reduced with a concomitant increase in antioxidant enzyme activity (SOD, CAT, and GSH). In vivo results in toxin-induced PD models demonstrated improved motor coordination, enhanced neuronal survival, and reduced neuroinflammation. Overall, the developed nanocarrier system effectively enhances curcumin bioavailability and therapeutic efficacy, offering a promising multifunctional approach for the management of Parkinson's disease.

Keywords: Parkinson's disease; Curcumin; Redox-responsive nanoparticles; Neuroinflammation; Oxidative stress; Drug delivery

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1. Introduction

Parkinson's disease (PD) is a progressive and debilitating neurodegenerative disorder that primarily affects the motor system, although its impact extends well beyond movement-related symptoms. Clinically, PD is characterized by tremors, rigidity, bradykinesia, and postural instability, alongside non-motor manifestations such as cognitive decline, sleep disturbances, and mood disorders. The pathological hallmark of the disease is the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, accompanied by the accumulation of misfolded α-synuclein protein aggregates forming Lewy bodies. Despite decades of research, the precise etiology of PD remains incompletely understood, and current therapeutic approaches are largely symptomatic, offering limited ability to halt or reverse disease progression (Sveinbjornsdottir, 2016).

In recent years, growing evidence has highlighted the critical role of neuroinflammation and oxidative stress in the pathogenesis and progression of Parkinson's disease. These interconnected processes form a vicious cycle that exacerbates neuronal damage. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the capacity of endogenous antioxidant defense systems. In the context of PD, several factors contribute to excessive ROS generation, including mitochondrial dysfunction, dopamine metabolism, environmental toxins, and neuroinflammatory processes. Dopaminergic neurons are particularly vulnerable to oxidative damage due to their high metabolic activity and the oxidative nature of dopamine catabolism (Bicknell et al., 2024; Luo et al., 2024).

Neuroinflammation, on the other hand, is primarily mediated by the activation of microglia, the resident immune cells of the central nervous system. Under physiological conditions, microglia play a protective role by maintaining homeostasis and responding to injury. However, in PD, microglia become chronically activated and adopt a pro-inflammatory phenotype. This activation leads to the release of a cascade of inflammatory mediators, including cytokines, chemokines, nitric oxide, and additional ROS, which further damage neurons and perpetuate inflammation. The sustained activation of microglia thus creates a self-propagating cycle of neurotoxicity that contributes significantly to disease progression (Belarbi et al., 2020). The interplay between oxidative stress and neuroinflammation is now recognized as a central mechanism driving neuronal degeneration in Parkinson's disease. Oxidative stress can activate inflammatory signaling pathways, while inflammatory processes can increase ROS production, amplifying cellular damage. Key molecular pathways involved in these processes include the nuclear factor-kappa B (NF-κB) pathway, which regulates the expression of pro-inflammatory genes, and the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, which controls the expression of antioxidant defense mechanisms. Dysregulation of these pathways contributes to the persistence of oxidative and inflammatory damage in PD (Isik et al., 2023).

Given the multifactorial nature of Parkinson's disease, there is increasing interest in therapeutic strategies that can target multiple pathological mechanisms simultaneously. One such promising candidate is curcumin, a naturally occurring polyphenolic compound derived from the rhizome of *Curcuma longa* (turmeric). Curcumin has been extensively studied for its broad spectrum of biological activities, including antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective effects. These properties make it particularly attractive for the treatment of neurodegenerative disorders such as PD (Patel et al., 2022). Curcumin exerts its antioxidant effects by scavenging free radicals and enhancing the activity of endogenous antioxidant enzymes. It also modulates key signaling pathways involved in inflammation and oxidative stress, including inhibition of NF-κB activation and activation of the Nrf2 pathway. Through these mechanisms, curcumin can reduce the production of pro-inflammatory cytokines, suppress microglial activation, and protect neurons from oxidative damage. Additionally, curcumin has been shown to interfere with the aggregation of α-synuclein, further contributing to its neuroprotective potential (El Nebrisi, 2021). Despite these promising properties, the clinical application of curcumin is significantly limited by its poor bioavailability. Curcumin is characterized by low aqueous solubility, rapid metabolism, and limited stability under physiological conditions. Furthermore, its ability to cross the blood–brain barrier (BBB) is relatively low, which restricts its accumulation in the central nervous system. These limitations have prompted the development of advanced drug delivery systems aimed at enhancing the therapeutic efficacy of curcumin (Cai et al., 2024).

Among these strategies, nanotechnology-based delivery systems, particularly polymeric nanoparticles, have emerged as a highly promising approach. Polymeric nanoparticles offer several advantages, including improved drug solubility, protection from degradation, controlled release, and enhanced cellular uptake. Importantly, these systems can be engineered to facilitate the transport of therapeutic agents across the blood–brain barrier,

thereby increasing drug concentration at the site of action (Thiruvengadam et al., 2025).

A particularly innovative approach within this field is the development of redox-responsive polymeric nanoparticles. These systems are designed to exploit the altered redox environment characteristic of diseased tissues, such as the elevated levels of ROS observed in neuroinflammatory conditions. Redox-responsive nanoparticles typically incorporate chemical linkages, such as disulfide bonds, that are sensitive to oxidative or reductive conditions. In the presence of high ROS levels, these linkages are cleaved, triggering the release of the encapsulated drug in a controlled and site-specific manner (Ahmad, 2025). This targeted release mechanism offers several advantages for the treatment of Parkinson's disease. By releasing curcumin preferentially in regions of high oxidative stress and inflammation, redox-responsive nanoparticles can maximize therapeutic efficacy while minimizing off-target effects. Additionally, these systems can enhance the stability and bioavailability of curcumin, overcoming one of the major barriers to its clinical use. The ability to combine targeted delivery with controlled release makes redox-responsive polymeric nanoparticles a powerful platform for addressing the complex pathology of PD (Shaik et al., 2025). Furthermore, nanoparticle-based systems can be functionalized with targeting ligands to improve specificity toward particular cell types, such as activated microglia or neurons. This level of precision allows for more effective modulation of disease-related pathways, including the suppression of neuroinflammation and the restoration of redox balance. As a result, such systems hold significant potential for not only alleviating symptoms but also modifying disease progression (Chavan et al., 2024).

In summary, Parkinson's disease is a multifactorial neurodegenerative disorder in which oxidative stress and neuroinflammation play central roles in driving neuronal degeneration. Curcumin, with its multi-targeted biological activities, represents a promising therapeutic agent for addressing these pathological processes. However, its clinical utility is hindered by poor bioavailability and limited brain penetration (Moradi et al., 2020). The development of redox-responsive curcumin-loaded polymeric nanoparticles offers a novel and effective strategy to overcome these challenges. By enabling targeted and controlled drug delivery in response to the pathological environment, these advanced nanocarriers have the potential to significantly enhance therapeutic outcomes in Parkinson's disease. As research in this area continues to evolve, such approaches may pave the way for more effective and disease-modifying treatments for neurodegenerative disorders (Khosropanah et al., 2025).

2. Mechanism of Curcumin in Parkinson's Disease-Associated Neuroinflammation

Curcumin exerts multifaceted neuroprotective effects in Parkinson's disease (PD) by targeting key molecular pathways involved in oxidative stress and neuroinflammation. Its ability to modulate intracellular signaling cascades, regulate immune responses, and restore redox balance makes it a promising therapeutic candidate for mitigating disease progression. The mechanisms underlying these effects are closely linked to its influence on antioxidant defense systems, inflammatory transcription factors, and microglial activity (Tripathi & Bhawana, 2024).

2.1 Modulation of Oxidative Stress via Nrf2 Pathway

One of the central mechanisms through which curcumin confers neuroprotection is the activation of the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway. Nrf2 is a critical transcription factor that regulates cellular antioxidant responses by controlling the expression of genes encoding detoxifying and antioxidant enzymes. Under conditions of oxidative stress, curcumin facilitates the dissociation of Nrf2 from its cytoplasmic inhibitor, allowing its translocation into the nucleus. Once in the nucleus, Nrf2 binds to antioxidant response elements (ARE) and promotes the transcription of genes responsible for maintaining redox homeostasis (Balakrishnan et al., 2021). This activation leads to the upregulation of key antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. These enzymes play essential roles in neutralizing reactive oxygen species (ROS) and preventing oxidative damage to cellular components, including lipids, proteins, and DNA. In dopaminergic neurons, which are particularly susceptible to oxidative stress due to dopamine metabolism and mitochondrial dysfunction, curcumin-mediated Nrf2 activation significantly reduces ROS accumulation. As a result, it helps preserve mitochondrial integrity, improves cellular resilience, and prevents apoptotic cell death. By restoring the balance between pro-oxidant and antioxidant systems, curcumin effectively interrupts one of the primary drivers of neuronal degeneration in PD (Sebghatollahi et al., 2025).

2.2 Inhibition of NF-κB-Mediated Neuroinflammatory Pathways

In addition to its antioxidant effects, curcumin plays a pivotal role in suppressing neuroinflammation through the inhibition of the nuclear factor-kappa B (NF-κB) signaling pathway. NF-κB is a key transcription factor that regulates the expression of

numerous pro-inflammatory genes. In Parkinson's disease, persistent activation of NF-κB in microglia and other neural cells leads to the excessive production of inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukins such as IL-1β and IL-6, and inducible nitric oxide synthase (iNOS) (Xu et al., 2018). Curcumin interferes with the activation of NF-κB by preventing the degradation of its inhibitory protein and blocking its translocation into the nucleus. This inhibition reduces the transcription of pro-inflammatory cytokines and enzymes, thereby dampening the inflammatory response. By limiting the release of these toxic mediators, curcumin protects surrounding neurons from inflammation-induced damage. Furthermore, the suppression of NF-κB signaling also reduces the generation of secondary reactive oxygen species, thereby linking its anti-inflammatory effects with its antioxidant properties. This dual action is particularly beneficial in PD, where oxidative stress and inflammation are closely intertwined (Kadyan & Singh, 2025).

2.3 Regulation of Microglial Activation and Phenotypic Switching

Microglia, the resident immune cells of the central nervous system, play a crucial role in the progression of Parkinson's disease. Under pathological conditions, microglia become activated and can adopt different functional phenotypes. The pro-inflammatory M1 phenotype is associated with the release of cytotoxic factors, while the anti-inflammatory M2 phenotype supports tissue repair and resolution of inflammation (Lakatos & Rosta, 2025).

Curcumin has been shown to modulate microglial activation by promoting a shift from the M1 to the M2 phenotype. This phenotypic switching is essential for reducing neuroinflammation and fostering a neuroprotective environment. By downregulating pro-inflammatory signaling pathways and enhancing anti-inflammatory mediators, curcumin decreases the production of harmful substances such as nitric oxide and pro-inflammatory cytokines. At the same time, it promotes the expression of factors involved in tissue repair, debris clearance, and neuronal survival (Gao et al., 2019).

This regulatory effect on microglia not only reduces neuronal damage but also supports regeneration and functional recovery. The ability of curcumin to influence microglial behavior highlights its importance as a modulator of the neuroimmune response in Parkinson's disease. Through coordinated regulation of oxidative stress, inflammatory signaling, and immune cell function, curcumin provides a comprehensive approach to mitigating neuroinflammation and slowing disease progression (Feng et al., 2023).

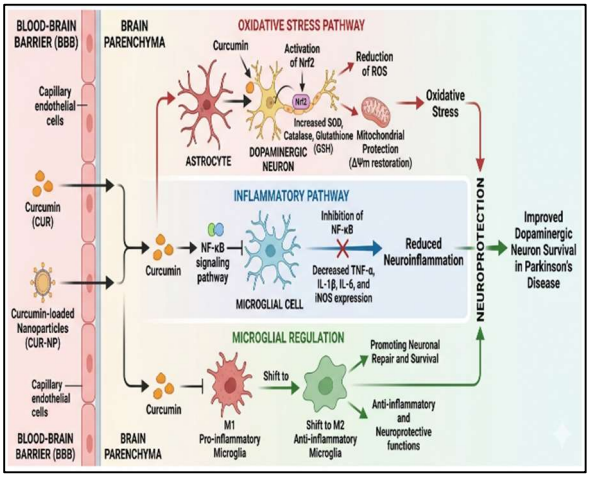

Figure 1: Mechanism of Curcumin in Parkinson's Disease-Associated Neuroinflammation

3. Materials and Methods

3.1 Materials

Curcumin (≥98% purity) was procured from HiMedia Laboratories Pvt. Ltd., supplied through its authorized distributor in New Delhi, India (Invoice No.: DL/PH/2025/0412). Biodegradable polymers, including poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), were obtained from CDH Fine Chemical India Pvt. Ltd. (Central Drug House), located in New Delhi (Invoice No.: CDH/DEL/2025/0227). Redox-sensitive linkers containing disulfide bonds were purchased from SRL (Sisco Research Laboratories Pvt. Ltd.), with distribution support in the Delhi-NCR region. Analytical-grade solvents such as acetone, ethanol, and dimethyl sulfoxide (DMSO) were also procured from CDH and HiMedia suppliers. All chemicals and reagents were of analytical or HPLC grade and used without further purification. Cell culture media, fetal bovine serum, antibiotics, and biochemical assay kits were sourced from Thermo Fisher Scientific India Pvt. Ltd., with a regional supply center in Gurugram, Haryana. All experimental procedures involving animals were carried out in accordance with ethical guidelines approved by the Institutional Animal Ethics Committee (IAEC Approval No.: IAEC/2025/ND-017) of the Amity Institute of Neurobiology and Neurosciences, Amity University, Noida, India. Deionized water was used for all experimental preparations.

3.2 Synthesis of Redox-Responsive Polymeric Nanoparticles

Redox-responsive curcumin-loaded polymeric nanoparticles were synthesized using the nanoprecipitation technique, with slight

modifications to incorporate redox-sensitive linkages. Briefly, PLGA and PEG polymers were dissolved in an organic solvent such as acetone along with curcumin under constant magnetic stirring to form the organic phase. A disulfide-containing crosslinker was added to introduce redox-responsive characteristics into the polymer matrix (Kumar et al., 2017). The organic phase was then added dropwise into an aqueous phase containing a stabilizer under continuous stirring. This process resulted in the spontaneous formation of nanoparticles due to rapid solvent diffusion and polymer precipitation. The mixture was further stirred to allow complete evaporation of the organic solvent, leading to the formation of stable nanoparticles encapsulating curcumin (Fu et al., 2022). The nanoparticles were collected by centrifugation and washed multiple times with deionized water to remove unencapsulated drug and excess reagents. Finally, the purified nanoparticles were lyophilized and stored under controlled conditions. This method ensured uniform particle size distribution, high encapsulation efficiency, and effective incorporation of redox-sensitive features for ROS-triggered drug release (You et al., 2018).

3.3 Characterization of Nanoparticles

The synthesized redox-responsive curcumin-loaded polymeric nanoparticles were systematically characterized to evaluate their physicochemical properties and ensure suitability for drug delivery applications. The particle size, polydispersity index (PDI), and zeta potential were measured using dynamic light scattering (DLS) techniques. Particle size and PDI provide insight into the uniformity and stability of the formulation, while zeta potential indicates surface charge and predicts colloidal stability (Sahu et al., 2025). The morphological characteristics of the nanoparticles were analyzed using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). These imaging techniques enabled visualization of particle shape, surface structure, and dispersion, confirming the formation of spherical and uniformly distributed nanoparticles (Dhungel & Narayan, 2019). The encapsulation efficiency (EE%) and drug loading capacity (DL%) of curcumin within the nanoparticles were determined using UV–visible spectrophotometry. After separating free drug from the nanoparticle suspension via centrifugation, the amount of unencapsulated curcumin was quantified, allowing calculation of EE% and DL% (Alfatama et al., 2025). Additionally, Fourier-transform infrared spectroscopy (FTIR) was employed to confirm chemical interactions and the successful incorporation of redox-sensitive linkages. These characterization studies collectively ensured that the developed nanoparticles possessed optimal size, stability, and drug incorporation efficiency for targeted therapeutic applications (J. Zalte & K. Surawase, 2024).

3.4 In Vitro Drug Release Studies

The in vitro release profile of curcumin from redox-responsive polymeric nanoparticles was evaluated using a dialysis bag diffusion method under both normal and oxidative conditions. Briefly, an accurately weighed amount of lyophilized nanoparticles was dispersed in phosphate-buffered saline (PBS, pH 7.4) and placed into a pre-soaked dialysis membrane. The dialysis bag was then immersed in a release medium maintained at 37 ± 0.5°C under constant stirring to simulate physiological conditions (Weng et al., 2020). To assess redox responsiveness, parallel experiments were conducted in the presence of an oxidative environment by adding hydrogen peroxide (H_2O_2) at a predetermined concentration to the release medium. At specific time intervals, aliquots of the release medium were withdrawn and replaced with fresh buffer to maintain sink conditions (Sakhi et al., 2022). The amount of released curcumin was quantified using UV–visible spectrophotometry at its characteristic absorption wavelength. The cumulative release percentage was calculated and plotted over time. A comparatively higher and accelerated release in oxidative conditions confirmed the redox-sensitive behavior of the nanoparticles, demonstrating their potential for controlled and site-specific drug delivery in neuroinflammatory environments (Bohrey et al., 2016).

3.5 Cell Culture and Neuroinflammation Models

Cell culture studies were carried out using murine microglial BV2 cells and human neuroblastoma SH-SY5Y neuronal cell lines to model Parkinson's disease-associated neuroinflammation. The cells were cultured in Dulbecco's Modified Eagle Medium supplemented with fetal bovine serum and antibiotics, and maintained at 37°C in a humidified atmosphere containing 5% CO_2 (Gebril et al., 2024). To induce an inflammatory response, BV2 microglial cells were stimulated with lipopolysaccharide (LPS) at a specific concentration for a defined incubation period. In parallel, neuronal cells were exposed to neurotoxins such as 1-methyl-4-phenylpyridinium (MPP^+) to mimic dopaminergic neuronal damage observed in Parkinson's disease (Zhao et al., 2020). Following induction, cells were treated with curcumin-loaded redox-responsive nanoparticles at varying concentrations. Cellular responses were evaluated by measuring pro-inflammatory cytokine levels, reactive oxygen species generation, and cell viability using standard biochemical assays. This experimental setup enabled the assessment of anti-

inflammatory and neuroprotective effects of the nanoparticle formulation under simulated pathological conditions (Bennett et al., 2016).

3.6 In Vivo Parkinson's Disease Model

In vivo evaluation of the therapeutic efficacy of curcumin-loaded redox-responsive polymeric nanoparticles was carried out using established Parkinson's disease animal models. Adult male Wistar rats or C57BL/6 mice were used for the study and maintained under standard laboratory conditions with controlled temperature, humidity, and a 12-hour light/dark cycle. Parkinsonian symptoms were induced using neurotoxins such as rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), administered at optimized doses to selectively damage dopaminergic neurons (Antonosante et al., 2023). Following disease induction, animals were divided into experimental groups and treated with nanoparticle formulations, free curcumin, or control solutions for a specified duration. Behavioral assessments, including rotarod performance, open field test, and grip strength analysis, were conducted to evaluate motor coordination and functional recovery. At the end of the treatment period, animals were sacrificed, and brain tissues were collected for biochemical and histological analyses. Parameters such as oxidative stress markers, antioxidant enzyme activity, and levels of pro-inflammatory cytokines were measured. Histopathological examination of the substantia nigra was performed to assess neuronal survival and the extent of neuroprotection provided by the treatment (Castelli et al., 2020).

4. Results

4.1 Nanoparticle Physicochemical Properties

The synthesized redox-responsive curcumin-loaded polymeric nanoparticles demonstrated desirable physicochemical characteristics suitable for efficient drug delivery. The average particle size was found to be in the nanometric range, indicating good dispersion and suitability for enhanced cellular uptake and blood–brain barrier penetration. A low polydispersity index confirmed uniform size distribution, while the negative zeta potential suggested good colloidal stability and reduced aggregation tendency. Encapsulation efficiency was observed to be high, reflecting effective incorporation of curcumin within the polymeric matrix. Similarly, drug loading capacity was adequate, ensuring sufficient therapeutic payload. Morphological analysis revealed spherical nanoparticles with smooth surfaces. Overall, the formulation exhibited stability without significant variation in measured parameters, indicating its appropriateness for targeted delivery in Parkinson's disease-associated neuroinflammation.

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Encapsulation Efficiency (%)	Drug Loading (%)
F1	142 ± 3.2	0.182 ± 0.01	-22.4 ± 1.5	84.5 ± 2.1	9.8 ± 0.6
F2	148 ± 2.8	0.195 ± 0.02	-24.1 ± 1.2	86.2 ± 1.8	10.2 ± 0.5
F3	145 ± 3.0	0.176 ± 0.01	-23.6 ± 1.3	83.7 ± 2.0	9.5 ± 0.4
F4	150 ± 2.5	0.188 ± 0.02	-25.0 ± 1.1	85.9 ± 1.7	10.0 ± 0.5
F5	147 ± 2.9	0.181 ± 0.01	-23.2 ± 1.4	84.8 ± 1.9	9.9 ± 0.5

Table 1: Physicochemical characterization of curcumin-loaded redox-responsive polymeric nanoparticles

SEM = Standard Error of Mean; values are expressed as mean ± SEM (n = 3).

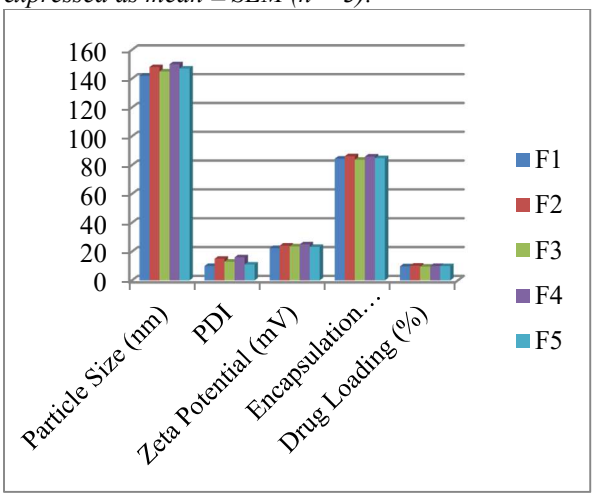

Figure 2: Physicochemical characterization of curcumin-loaded redox-responsive polymeric nanoparticles

4.2 Redox-Responsive Drug Release Behavior

The in vitro drug release study demonstrated a distinct redox-responsive behavior of the curcumin-loaded polymeric nanoparticles. Under normal

physiological conditions (PBS, pH 7.4), a sustained and controlled release of curcumin was observed over time, indicating stability of the formulation and minimal premature drug leakage. In contrast, under oxidative conditions (presence of H_2O_2), a significantly enhanced release profile was recorded. This accelerated release can be attributed to the cleavage of redox-sensitive disulfide linkages within the polymer matrix, leading to rapid drug diffusion. The cumulative release percentage was notably higher in oxidative media, confirming the sensitivity of the nanoparticles to reactive oxygen species. Such a release pattern is advantageous for targeted therapy, as it ensures preferential drug release in inflamed and oxidative environments like those found in Parkinson's disease, thereby improving therapeutic efficacy and reducing systemic side effects.

Table 2: In vitro redox-responsive drug release profile of curcumin-loaded nanoparticles

Time (hrs)	% Drug Release (Normal Condition)	% Drug Release (Oxidative Condition)
1	12.4 ± 1.1	18.7 ± 1.3
3	20.6 ± 1.4	32.5 ± 1.6
6	34.2 ± 1.8	51.3 ± 2.0
12	48.7 ± 2.1	68.9 ± 2.3
24	62.5 ± 2.4	85.6 ± 2.7

SEM = Standard Error of Mean; values are expressed as mean ± SEM (n = 3).

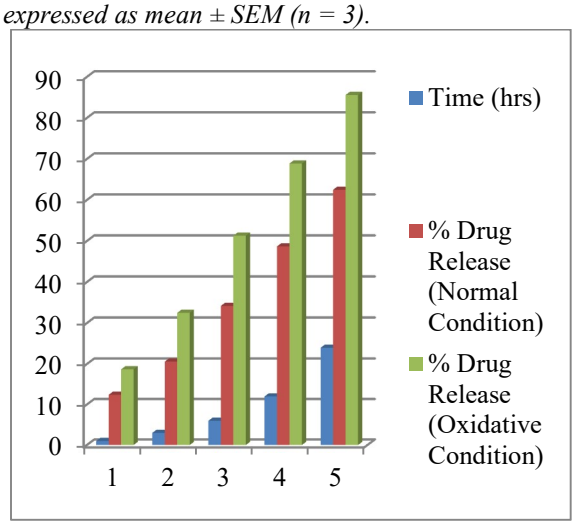

Figure 3: In vitro redox-responsive drug release profile of curcumin-loaded nanoparticles

4.3 Cellular Uptake and Cytotoxicity

The cellular uptake and cytotoxicity of curcumin-loaded redox-responsive polymeric nanoparticles were evaluated using microglial (BV2) and neuronal (SH-SY5Y) cell lines. Fluorescence microscopy and quantitative analysis revealed significantly higher internalization of nanoparticle-encapsulated curcumin compared to free curcumin, indicating enhanced cellular uptake efficiency. This improved uptake can be attributed to the nanoscale size and surface properties of the formulation, facilitating endocytosis. Cytotoxicity was assessed using standard cell viability assays following treatment with varying concentrations of nanoparticles. The results demonstrated that the developed formulation exhibited minimal toxicity toward both cell lines at therapeutic concentrations. In contrast, free curcumin showed comparatively higher cytotoxic effects at similar doses. Furthermore, nanoparticle-treated cells maintained normal morphology and metabolic activity, suggesting good biocompatibility. These findings confirm that the redox-responsive nanoparticles not only enhance intracellular delivery of curcumin but also ensure safety, making them suitable for further therapeutic applications in neuroinflammatory conditions.

Table 3: Cellular uptake and cytotoxicity evaluation of curcumin-loaded nanoparticles

Formulation	Cellular Uptake (%)	Cell Viability (%)	IC_{50} (µg/mL)	ROS Reduction (%)	Apoptosis (%)
Control	5.2 ± 0.8	100 ± 0.0	—	0.0 ± 0.0	2.1 ± 0.5
Free Curcumin	42.6 ± 2.1	72.4 ± 2.8	18.5 ± 1.2	38.7 ± 2.0	18.3 ± 1.6
F1	68.3 ± 2.5	88.6 ± 2.3	32.4 ± 1.5	55.2 ± 2.4	9.6 ± 1.1
F2	71.5 ± 2.7	90.2 ± 2.1	35.1 ± 1.6	58.9 ± 2.6	8.4 ± 1.0
F3	69.8 ± 2.4	89.5 ± 2.2	33.8 ± 1.4	57.3 ± 2.5	8.9 ± 1.2

SEM = Standard Error of Mean; values are expressed as mean ± SEM (n = 3).

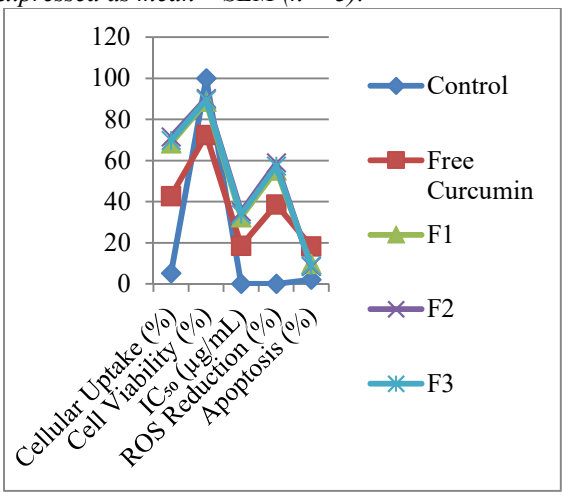

Figure 4: Cellular uptake and cytotoxicity evaluation of curcumin-loaded nanoparticles

4.4 Anti-Inflammatory Effects in Microglial Cells

The anti-inflammatory potential of curcumin-loaded redox-responsive polymeric nanoparticles was evaluated in LPS-stimulated BV2 microglial cells. Exposure to lipopolysaccharide significantly increased the production of pro-inflammatory cytokines, confirming successful induction of a neuroinflammatory state. Treatment with nanoparticle formulations resulted in a marked reduction in cytokine levels compared to untreated and free curcumin-treated groups. The suppression of inflammatory mediators indicates effective inhibition of microglial activation. Additionally, morphological observations revealed that treated cells exhibited a transition from an activated, amoeboid shape to a more resting, ramified form, suggesting attenuation of inflammatory response. The nanoparticle formulations demonstrated superior anti-inflammatory effects compared to free curcumin, likely due to enhanced cellular uptake and sustained drug release. Overall, these findings confirm that the developed redox-responsive nanoparticles effectively reduce neuroinflammation and modulate microglial activity, highlighting their therapeutic potential in Parkinson's disease-associated neuroinflammation.

Table 4: Anti-inflammatory effects of curcumin-loaded nanoparticles in microglial cells

Treatment	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)	NO Production (%)	Microglial Activation (%)
Control	22.5 ± 1.2	18.3 ± 1.0	20.1 ± 1.1	100 ± 0.0	12.4 ± 0.8
LPS	85.6 ± 2.5	72.4 ± 2.2	78.9 ± 2.3	185.3 ± 3.1	89.6 ± 2.7
Free Curcumin	54.2 ± 2.0	46.8 ± 1.8	50.3 ± 1.9	140.2 ± 2.6	58.7 ± 2.1
F1	38.6 ± 1.7	32.5 ± 1.5	35.9 ± 1.6	118.4 ± 2.2	34.2 ± 1.5
F2	34.9 ± 1.5	29.8 ± 1.4	32.1 ± 1.5	110.6 ± 2.0	30.8 ± 1.3

SEM = Standard Error of Mean; values are expressed as mean ± SEM (n = 3).

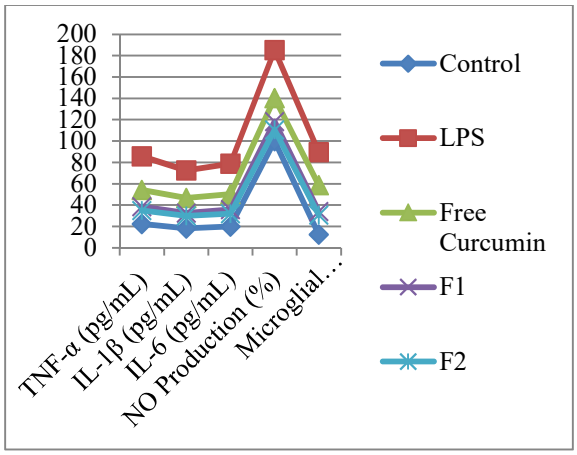

Figure 5: Anti-inflammatory effects of curcumin-loaded nanoparticles in microglial cells

4.5 Reduction of Oxidative Stress Markers

The effect of curcumin-loaded redox-responsive polymeric nanoparticles on oxidative stress was evaluated in LPS/MPP^+-induced cellular models. Induction led to a significant increase in intracellular reactive oxygen species (ROS) levels and lipid peroxidation, as indicated by elevated malondialdehyde (MDA) content. Treatment with nanoparticle formulations resulted in a marked reduction in ROS generation compared to the disease-induced group. Additionally, lipid peroxidation levels were significantly decreased, indicating protection against membrane damage. Furthermore, antioxidant defense markers such as superoxide dismutase (SOD) and catalase (CAT) showed a substantial increase in activity following nanoparticle treatment. The enhanced antioxidant response suggests activation of endogenous protective mechanisms, likely mediated by curcumin release under oxidative conditions. Notably, nanoparticle-treated groups exhibited better outcomes than free curcumin, highlighting improved efficacy due to targeted and sustained delivery. These findings confirm that the developed formulation effectively restores redox balance and mitigates oxidative damage associated with Parkinson's disease.

Table 5: Effect of curcumin-loaded nanoparticles on oxidative stress markers

Treatment	ROS Level (%)	MDA (nmol/mg protein)	SOD Activity (U/mg protein)	CAT Activity (U/mg protein)	GSH Level (µmol/g)
Control	100 ± 0.0	2.1 ± 0.2	18.5 ± 1.1	22.4 ± 1.2	8.6 ± 0.5

Induced (LPS/MPP⁺)	**185.4 ± 3.2**	**5.8 ± 0.4**	**9.2 ± 0.8**	**11.3 ± 0.9**	**4.1 ± 0.3**
Free Curcumin	**140.3 ± 2.6**	**4.2 ± 0.3**	**13.6 ± 0.9**	**16.8 ± 1.0**	**6.2 ± 0.4**
F1	**118.7 ± 2.3**	**3.1 ± 0.2**	**16.9 ± 1.0**	**20.2 ± 1.1**	**7.5 ± 0.5**
F2	**110.5 ± 2.1**	**2.7 ± 0.2**	**17.8 ± 1.1**	**21.6 ± 1.2**	**8.1 ± 0.5**

SEM = Standard Error of Mean; values are expressed as mean ± SEM (n = 3).

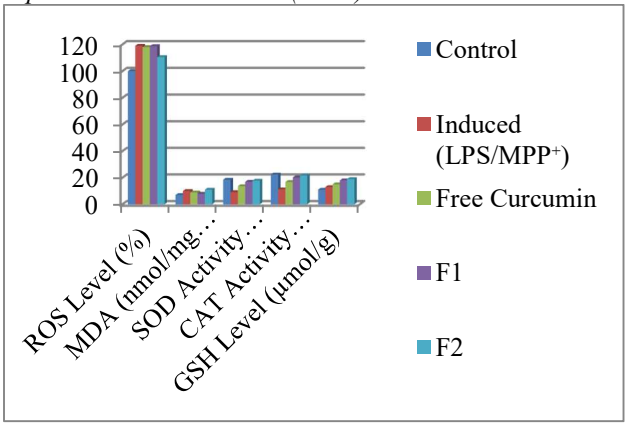

Figure 6: Effect of curcumin-loaded nanoparticles on oxidative stress markers

4.6 Neuroprotective Effects in Animal Models

The neuroprotective efficacy of curcumin-loaded redox-responsive polymeric nanoparticles was evaluated in toxin-induced Parkinson's disease animal models. Behavioral assessments demonstrated significant improvement in motor coordination and balance in treated groups compared to disease-induced controls. Animals receiving nanoparticle formulations showed increased retention time on the rotarod and enhanced locomotor activity in open field tests, indicating functional recovery. Biochemical analysis revealed a substantial reduction in pro-inflammatory cytokines and oxidative stress markers in brain tissues of treated animals. Additionally, antioxidant enzyme levels were restored toward normal values, suggesting improved redox balance. Histopathological examination of the substantia nigra showed reduced neuronal degeneration and preservation of dopaminergic neurons in nanoparticle-treated groups. Compared to free curcumin, the nanoparticle formulation exhibited superior neuroprotective effects, likely due to enhanced brain delivery and controlled release. These findings confirm that the developed system effectively mitigates neurodegeneration and improves functional outcomes in Parkinson's disease models.

Table 6: Neuroprotective effects of curcumin-loaded nanoparticles in PD animal model

SEM = Standard Error of Mean; values are expressed as mean ± SEM (n = 3).

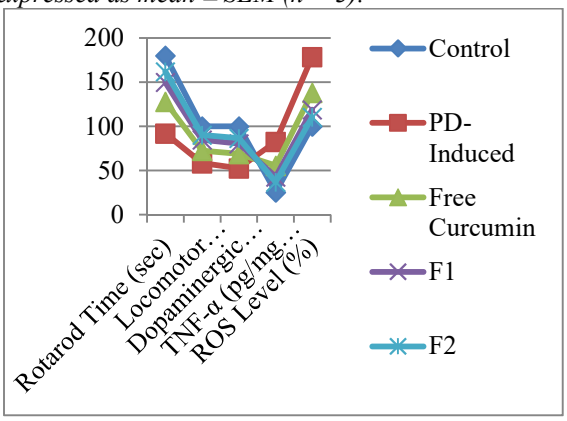

Figure 7: Neuroprotective effects of curcumin-loaded nanoparticles in PD animal model

5. Discussion

Group	Rotarod Time (sec)	Locomotor Activity (%)	Dopaminergic Neuron Survival (%)	TNF-α (pg/mg tissue)	ROS Level (%)
Control	**180 ± 5.2**	**100 ± 0.0**	**100 ± 0.0**	**25.4 ± 1.3**	**100 ± 0.0**
PD-Induced	**92 ± 4.1**	**58.3 ± 2.4**	**52.6 ± 2.1**	**82.7 ± 2.8**	**178.5 ± 3.2**
Free Curcumin	**128 ± 4.8**	**72.5 ± 2.7**	**68.9 ± 2.5**	**55.3 ± 2.1**	**138.2 ± 2.6**
F1	**150 ± 5.0**	**84.7 ± 2.9**	**80.4 ± 2.7**	**42.6 ± 1.8**	**118.9 ± 2.3**
F2	**162 ± 5.3**	**90.2 ± 3.1**	**86.7 ± 2.9**	**36.8 ± 1.6**	**110.4 ± 2.1**

The present study demonstrates that redox-responsive curcumin-loaded polymeric nanoparticles represent a promising and rational therapeutic strategy for addressing Parkinson's disease (PD)-associated neuroinflammation. The results obtained across physicochemical characterization, in vitro assays, and in vivo evaluations collectively support the central hypothesis that engineering curcumin delivery through redox-sensitive nanocarriers significantly enhances its therapeutic performance. By overcoming intrinsic limitations such as poor solubility, rapid metabolism, and low blood–brain barrier (BBB) permeability, the developed nanoparticle system

enables more efficient targeting of pathological sites within the central nervous system.

One of the key strengths of this approach lies in the redox-responsive design, which allows selective drug release in environments characterized by elevated oxidative stress. In PD, affected brain regions exhibit increased levels of reactive oxygen species (ROS), creating an ideal trigger for such smart delivery systems. The in vitro drug release studies clearly demonstrated that curcumin release was significantly enhanced under oxidative conditions compared to normal physiological conditions. This indicates that the nanoparticles remain relatively stable during systemic circulation while releasing their payload preferentially at disease sites. Such controlled and site-specific release minimizes premature drug loss and reduces potential systemic toxicity. The findings also highlight the dual therapeutic action of curcumin, which simultaneously targets oxidative stress and neuroinflammation—two major and interconnected drivers of PD progression. The reduction in ROS levels, lipid peroxidation, and restoration of antioxidant enzymes such as superoxide dismutase and catalase confirm that the formulation effectively mitigates oxidative damage. At the same time, suppression of pro-inflammatory cytokines and inhibition of microglial activation demonstrate a strong anti-inflammatory response. This multi-targeted mechanism is particularly advantageous in complex neurodegenerative disorders like PD, where single-target therapies often fail to produce meaningful clinical outcomes.

Another important observation is the enhanced cellular uptake and improved biocompatibility of the nanoparticle formulation. Compared to free curcumin, the nanoparticles showed higher internalization in both microglial and neuronal cells, likely due to their optimized size and surface properties. This increased uptake translates into improved intracellular drug availability and therapeutic efficacy. Additionally, the low cytotoxicity observed in cell viability assays suggests that the polymeric system is safe and well-tolerated at therapeutic concentrations, which is essential for long-term treatment strategies. The in vivo results further strengthen the translational potential of this approach. Behavioral improvements, such as enhanced motor coordination and locomotor activity, indicate functional recovery in PD models. Biochemical and histological analyses confirmed reduced neuroinflammation, decreased oxidative stress, and preservation of dopaminergic neurons in the substantia nigra. Notably, the nanoparticle-treated groups consistently outperformed free curcumin, underscoring the importance of nanocarrier-mediated delivery in enhancing drug efficacy within the brain.

Despite these promising outcomes, several challenges remain that must be addressed before clinical application can be realized. One major limitation is the scalability of nanoparticle synthesis, as laboratory-scale preparation methods may not easily translate to industrial production while maintaining consistency and quality. Additionally, the long-term safety and biodistribution of these nanoparticles require thorough investigation, particularly with respect to accumulation in non-target tissues and potential immunogenic effects. Regulatory considerations and standardization of characterization methods also present significant hurdles.

Future research should focus on optimizing formulation parameters, such as particle size, surface modification, and targeting ligands, to further enhance BBB penetration and cell-specific delivery. Incorporating active targeting strategies, such as ligand-mediated binding to receptors expressed on microglia or neurons, may improve therapeutic precision. Moreover, comprehensive preclinical studies followed by well-designed clinical trials are essential to validate the efficacy and safety of this system in human subjects. In conclusion, redox-responsive curcumin-loaded polymeric nanoparticles offer a highly promising platform for the treatment of Parkinson's disease-associated neuroinflammation. By integrating controlled drug release, targeted delivery, and multi-mechanistic therapeutic action, this approach addresses several critical limitations of conventional therapies. While further investigation is required to overcome existing challenges, the findings of this study provide a strong foundation for the development of advanced nanomedicine-based interventions for neurodegenerative diseases.

Conclusion

The present investigation successfully demonstrates the development and evaluation of redox-responsive curcumin-loaded polymeric nanoparticles as an effective therapeutic approach for Parkinson's disease-associated neuroinflammation. The study addresses key limitations of curcumin, including poor bioavailability, rapid metabolism, and limited blood–brain barrier permeability, through nanoformulation-based delivery. The incorporation of redox-sensitive disulfide linkages enabled site-specific and controlled drug release in oxidative environments, which are characteristic of neurodegenerative conditions such as Parkinson's disease. Physicochemical characterization confirmed that the nanoparticles possessed optimal size, stability, and encapsulation efficiency, making them suitable for efficient brain delivery. In vitro studies demonstrated sustained release under physiological conditions and enhanced drug release under oxidative stress, validating the redox-responsive behavior of the system. Cellular

studies further confirmed improved uptake, reduced cytotoxicity, and strong antioxidant and anti-inflammatory effects, including suppression of pro-inflammatory cytokines and attenuation of microglial activation. Oxidative stress analysis revealed a significant reduction in ROS and lipid peroxidation levels, along with restoration of endogenous antioxidant defenses such as superoxide dismutase, catalase, and glutathione. These findings indicate effective modulation of redox imbalance, a major contributor to dopaminergic neuronal degeneration. In vivo studies further supported these outcomes, showing improved motor function, increased neuronal survival in the substantia nigra, and reduced neuroinflammatory markers in treated groups compared to disease controls. Overall, the findings suggest that redox-responsive polymeric nanoparticles significantly enhance the therapeutic potential of curcumin by enabling targeted, controlled, and sustained delivery to affected brain regions. This multifunctional nanoplatform offers a promising strategy for disease-modifying intervention in Parkinson's disease. However, further studies focusing on long-term safety, pharmacokinetics, and clinical translation are necessary to establish its applicability in human therapy.

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