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Development and Evaluation of Targeted Antihypertensive Therapy Using Losartan-Encapsulated Nanoparticles

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ABSTRACT

Hypertension is a widespread chronic condition and a major risk factor for cardiovascular diseases. Losartan, an angiotensin II receptor blocker, is commonly prescribed due to its efficacy and favorable safety profile. However, its therapeutic application is limited by poor oral bioavailability (approximately 33%), rapid hepatic metabolism, and frequent dosing requirements. This study aims to develop and evaluate a targeted nanoparticle-based drug delivery system for Losartan to enhance its pharmacokinetic and therapeutic profile. Losartan-loaded nanoparticles were formulated using the solvent evaporation method with polymers including PLGA, chitosan, and PEG derivatives. Formulation optimization was achieved through Box-Behnken Design, enabling the selection of the best-performing formulation based on particle size, zeta potential, drug loading (DL%), and encapsulation efficiency (EE%). The optimized PLGA-based formulation (F2) exhibited a mean particle size of 182.7 nm, zeta potential of –24.6 mV, DL% of 11.2, and EE% of 86.4. SEM analysis confirmed spherical shape with smooth surface morphology and no aggregation. In vitro drug release studies demonstrated a biphasic profile with an initial burst followed by sustained release over 48 hours. Kinetic modeling identified the Higuchi model ($R^2 = 0.987$) as the best fit, indicating diffusion-controlled release, while the Korsmeyer–Peppas model showed an anomalous transport mechanism ($n = 0.61$). Stability studies under ICH-recommended conditions confirmed long-term physical and chemical stability. These findings suggest that Losartan-loaded PLGA nanoparticles offer a promising approach for sustained, targeted antihypertensive therapy with improved bioavailability and reduced dosing frequency.

Keywords: *Angiotensin receptor blocker, PLGA nanoparticles, targeted delivery, drug release kinetics, Losartan encapsulation, antihypertensive therapy*

1. INTRODUCTION

Hypertension, commonly known as high blood pressure, is one of the most prevalent chronic health conditions worldwide, affecting over 1.28 billion adults aged 30–79 years, according to the World Health Organization. It is a critical risk factor for cardiovascular diseases, stroke, renal dysfunction, and other serious health complications. Despite its widespread prevalence and the availability of effective medications, hypertension remains inadequately managed in many populations due to factors such as poor compliance, suboptimal pharmacokinetics of drugs, and systemic side effects (Mills et al., 2020). The asymptomatic nature of hypertension often leads to delayed diagnosis and inconsistent therapeutic adherence, further

exacerbating health risks. Consequently, enhancing the therapeutic management of hypertension through more efficient and targeted drug delivery strategies has become a key area of biomedical research (Zhou et al., 2021). Among the array of pharmacological agents used to manage hypertension, Losartan—a selective angiotensin II receptor type 1 (AT1) antagonist—has gained prominence due to its effective blood pressure-lowering effects, organ-protective properties, and a favorable side-effect profile compared to other classes such as beta-blockers or calcium channel blockers (Mocumbi et al., 2015). Losartan interferes with the renin-angiotensin-aldosterone system (RAAS), a hormonal cascade critical for blood pressure regulation and fluid balance. By blocking the AT1 receptor, Losartan inhibits vasoconstriction and reduces aldosterone-mediated sodium retention, thereby reducing blood pressure and alleviating strain on the cardiovascular system (Mills et al., 2016).

Despite these advantages, Losartan suffers from significant pharmacokinetic limitations that compromise its therapeutic efficiency. Notably, its oral bioavailability is relatively low, estimated at approximately 33%, primarily due to extensive first-pass hepatic metabolism. The metabolic conversion of Losartan to its active carboxylic acid metabolite (EXP3174) occurs rapidly, with the parent compound exhibiting a relatively short half-life (Ripley & Hirsch, 2010). This not only necessitates frequent dosing but also leads to variable plasma concentrations, which can compromise therapeutic efficacy and increase the risk of adverse effects. Additionally, the conventional oral route of administration exposes the drug to enzymatic degradation in the gastrointestinal tract, further diminishing its systemic availability (Puskarich et al., 2021). Given these limitations, there is a growing need for targeted delivery systems that can enhance the pharmacological performance of Losartan. Targeted drug delivery offers several critical advantages, including the ability to concentrate the therapeutic agent at the desired site of action while minimizing systemic exposure and associated side effects (Teixido-Tura et al., 2018). By bypassing or minimizing hepatic first-pass metabolism, targeted systems can improve drug bioavailability and provide more consistent plasma levels. This has led to an increased focus on nanotechnology-based delivery systems, which offer promising solutions for overcoming the limitations associated with conventional drug administration routes (Groenink et al., 2013).

Nanoparticles, due to their tunable physicochemical properties and small size (typically 1–1000 nm), have emerged as one of the most promising platforms for targeted drug delivery. These systems can encapsulate therapeutic agents, protect them from degradation, and ensure controlled and sustained release profiles (Ertas et al., 2021). Moreover, nanoparticles can be engineered to exploit passive targeting mechanisms—such as the enhanced permeability and retention (EPR) effect—commonly observed in diseased tissues like inflamed vasculature and tumors. This phenomenon allows nanoparticles to accumulate in target tissues due to leaky vasculature and impaired lymphatic drainage. In addition to passive targeting, nanoparticles can be functionalized with specific ligands to enable active targeting to cell surface receptors, offering a dual advantage in precision therapy (Tiwari et al., 2011). For antihypertensive drugs like Losartan, nanoparticle-based delivery presents a viable strategy to address the shortcomings of traditional formulations. Encapsulation of Losartan in nanoparticulate systems can potentially enhance its stability, reduce dosing frequency, and improve patient compliance. Furthermore, by adjusting the composition and surface characteristics of nanoparticles, it is possible to tailor their biodistribution, release kinetics, and targeting capabilities to align with therapeutic goals (Kommana et al., 2020).

In light of these benefits, the primary objective of this research is to develop Losartan-loaded nanoparticles and evaluate their potential in targeted antihypertensive therapy. The development process will involve the selection of appropriate polymeric or lipid-based carriers, optimization of formulation parameters, and characterization of the nanoparticles in terms of size, surface charge, drug loading efficiency, and release profile. The final formulation will be assessed in vitro and in vivo for its ability to deliver Losartan effectively to target tissues and maintain therapeutic plasma concentrations over an extended period (Moradifar et al., 2021). To provide a comprehensive background for this research, it is essential to review the existing landscape of antihypertensive drugs and the associated challenges in their delivery. Traditional antihypertensive medications encompass a wide range of pharmacological classes, including ACE inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics, and beta-blockers (Elendu et al., 2024). While these drugs have demonstrated efficacy in lowering blood pressure and reducing cardiovascular morbidity and mortality, their systemic administration is often accompanied by undesirable side effects such as electrolyte imbalances, bradycardia, or renal dysfunction. Furthermore, many antihypertensive drugs have short half-lives and require multiple daily dosing, which can hinder patient adherence, especially in asymptomatic cases (Elendu et al., 2023).

A growing body of literature highlights the potential of nanoparticle-mediated drug delivery to overcome these challenges. Various studies have investigated the use of polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) for the controlled and targeted delivery of antihypertensive agents. These delivery platforms have shown improved pharmacokinetic profiles, enhanced drug stability, and better therapeutic outcomes in preclinical models. Notably, the integration of targeting ligands, such as peptides or antibodies, on nanoparticle surfaces has enabled active targeting of specific tissues or cell types, thus reducing systemic side effects and improving drug localization (Handa et al., 2021). In the context of Losartan, several research efforts have explored the potential of nanotechnology to improve its delivery. For instance, Losartan-loaded PLGA (poly(lactic-co-glycolic acid)) nanoparticles have demonstrated sustained drug release, improved pharmacokinetics, and superior antihypertensive effects in animal models. Chitosan-based

nanoparticles, owing to their mucoadhesive and biodegradable properties, have also been employed for oral and nasal delivery of Losartan, with promising results in terms of drug absorption and bioavailability. Solid lipid nanoparticles and nanostructured lipid carriers have further contributed to this research by offering biocompatible and scalable platforms for lipophilic drug encapsulation and sustained release (Patil et al., 2015).

The selection of nanoparticle type is crucial and depends on various factors such as drug properties, route of administration, and therapeutic goals. PLGA nanoparticles, for example, are FDA-approved and widely used due to their biodegradability and ability to provide sustained drug release. Chitosan nanoparticles offer the additional advantage of enhancing drug permeation across mucosal barriers. SLNs and NLCs are attractive for their high drug loading capacity and ease of large-scale production. Each of these systems has distinct advantages and limitations that must be carefully considered during formulation development (Koo et al., 2024). Targeting mechanisms employed in nanoparticle-based delivery can be broadly categorized into passive and active targeting. Passive targeting relies on physiological features such as the EPR effect, which facilitates the accumulation of nanoparticles in tissues with abnormal vasculature. This mechanism is particularly relevant for conditions involving vascular inflammation, including hypertension-related vascular remodeling (Shah et al., 2023). Active targeting, on the other hand, involves the functionalization of nanoparticles with specific ligands—such as folate, transferrin, or angiotensin II peptides—that bind to receptors overexpressed on target cells. This approach allows for enhanced specificity and cellular uptake of the drug-loaded nanoparticles, improving therapeutic outcomes while minimizing off-target effects (Shah et al., 2023). In summary, the integration of nanotechnology into antihypertensive therapy holds great promise for enhancing drug efficacy, reducing side effects, and improving patient compliance. The development of Losartan-loaded nanoparticles represents a strategic effort to overcome the pharmacokinetic limitations of the drug and to harness the advantages of targeted and sustained drug delivery. This research aims to bridge the gap between traditional pharmacotherapy and advanced nanomedicine by formulating and evaluating a novel nanoparticulate system for the efficient and targeted treatment of hypertension (Elkomy et al., 2022).

2. FORMULATION AND SYNTHESIS OF LOSARTAN-LOADED NANOPARTICLES

The synthesis of losartan-loaded nanoparticles was performed using the solvent evaporation method, a robust and reproducible technique widely applied for encapsulating hydrophobic drugs within biodegradable polymer matrices. In this approach, losartan and the selected polymer, such as poly(lactic-co-glycolic acid) (PLGA) or chitosan, were first dissolved in an organic solvent like dichloromethane or acetone to create a homogeneous organic phase. This organic solution was then slowly introduced into an aqueous phase containing a stabilizer, typically polyvinyl alcohol (PVA), under constant mechanical stirring. The mixture formed an oil-in-water emulsion as the organic phase dispersed into nanodroplets (Yu et al., 2019). To ensure the formation of uniform nanoparticles, high-speed homogenization or ultrasonication was employed immediately after emulsification. These techniques reduce the size of emulsion droplets, which directly influences the final nanoparticle size. After the emulsion was formed, the system was subjected to magnetic stirring under reduced pressure to evaporate the organic solvent. As the solvent evaporated, the polymer precipitated, encapsulating the drug and forming solid nanoparticles (Singh et al., 2019).

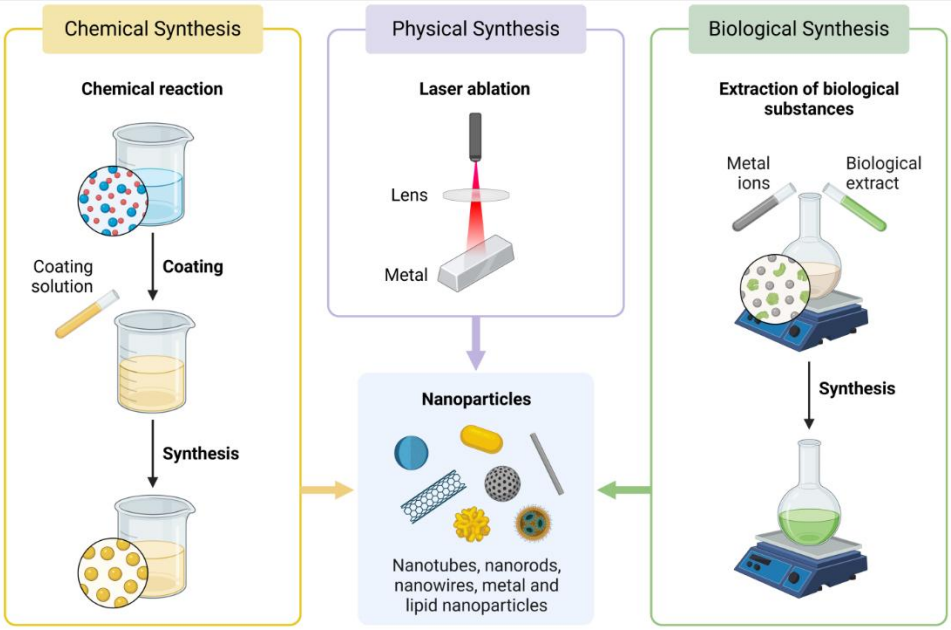

Figure 1: Basic Methods of Nanoparticle Synthesis

Several formulation variables were systematically optimized to achieve desirable characteristics, including particle size, polydispersity index (PDI), drug loading, and encapsulation efficiency. Parameters such as the polymer-to-drug ratio, stabilizer concentration, solvent type, and stirring speed were studied using a design of experiments (DoE) approach. A Box-Behnken Design (BBD) or full factorial design was applied to understand the interaction between these variables and to predict the optimum formulation conditions. This statistical modeling allowed for fine-tuning of the formulation with minimal trial-and-error, improving reproducibility and scalability (Aldawsari et al., 2023). Following synthesis, the nanoparticle suspension was collected and subjected to centrifugation to remove unentrapped drug and residual stabilizers. The resulting pellet was washed multiple times with distilled water to purify the formulation and was then lyophilized or freeze-dried to obtain a dry nanoparticulate powder for further analysis. Cryoprotectants like mannitol or trehalose were often added before freeze-drying to prevent nanoparticle aggregation and maintain stability during storage (Mikušová & Mikuš, 2021).

The prepared nanoparticles were then characterized for their physical and chemical properties. Particle size and zeta potential were analyzed using dynamic light scattering (DLS), which provided insights into dispersion uniformity and surface charge, respectively. A low PDI (<0.3) and a zeta potential value above ±20 mV typically indicated good colloidal stability. Morphological studies using Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM) confirmed the spherical shape and smooth surface of the particles (Jamous et al., 2023). Drug loading and encapsulation efficiency were evaluated by disrupting the nanoparticles using a solvent, followed by quantification of losartan using UV-Vis spectroscopy or High-Performance Liquid Chromatography (HPLC). FTIR and DSC analyses were performed to confirm drug-polymer compatibility and to assess the thermal behavior of the encapsulated drug. Overall, the solvent evaporation method provided a reliable and efficient route to formulate losartan-loaded nanoparticles with desirable physicochemical properties for targeted antihypertensive therapy (Carissimi et al., 2020).

3. MATERIALS AND METHODS

3.1. Materials

Losartan potassium, the active pharmaceutical ingredient used in this study, was obtained from Maya Biotech Pvt. Ltd., Baddi (HP), which supplies across NCR including Meerut via authorized distributors. This compound was selected for its clinical relevance in antihypertensive therapy. The polymer chitosan (medium molecular weight, 75–85% deacetylated) was sourced from Central Drug House (CDH), New Delhi, a widely used supplier in Northern India for pharmaceutical-grade materials. Chitosan was selected due to its excellent biocompatibility and mucoadhesive properties, making it ideal for nanoparticle formulation.

Analytical-grade acetone and ethanol, used as solvents for dissolving chitosan and drug substances, were procured from Loba Chemie Pvt. Ltd., Mumbai, but supplied locally by Shivam Scientifics, Meerut. These solvents were selected for their volatility and compatibility in the ionic gelation method. The surfactant polyvinyl alcohol (PVA) was purchased from Himedia Laboratories Pvt. Ltd., Mumbai, also distributed locally via Balaji Chemicals, Meerut. PVA plays a crucial role in stabilizing the nanoparticle suspension during synthesis. All materials were used without further purification and stored under recommended conditions. Ultrapure water used for all preparations was generated using a Merck Milli-Q water purification system installed in the laboratory at IIMT University, Meerut.

3.2. Preparation of Losartan-Loaded Nanoparticles

Losartan-loaded nanoparticles were prepared using the solvent evaporation technique, a well-established method for encapsulating hydrophobic drugs within biodegradable polymer matrices. In this process, losartan and the selected polymer (such as PLGA or chitosan) were dissolved in an organic solvent (e.g., dichloromethane or acetone) to form the organic phase. This solution was then emulsified into an aqueous phase containing a stabilizer like polyvinyl alcohol (PVA) under continuous stirring to form an oil-in-water emulsion. The emulsion was subsequently subjected to high-speed homogenization followed by solvent evaporation under reduced pressure, leading to nanoparticle formation (Khan et al., 2024).

Critical process parameters including stirring speed, polymer-to-drug ratio, and stabilizer concentration were systematically varied to achieve optimal particle size, drug loading, and encapsulation efficiency. The influence of these parameters was assessed using a statistical design of experiments approach. A Box-Behnken Design was employed to optimize formulation variables by evaluating the response surface for key outputs such as particle size and entrapment efficiency. The optimized formulation was selected based on desirability criteria ensuring uniformity, stability, and efficient drug release characteristics (Lamptey et al., 2023).

3.3. Surface Modification

To enhance the targeting efficiency and systemic stability of the losartan-loaded nanoparticles, surface modification was carried out through ligand conjugation techniques. Polyethylene glycol (PEG) was employed for PEGylation, a widely used strategy to increase circulation time, reduce opsonization, and prevent rapid clearance by the reticuloendothelial system. The

PEGylation process involved the covalent attachment of methoxy-PEG-NHS to the surface functional groups (e.g., amines or carboxyl groups) present on the polymeric nanoparticles (Jazayeri et al., 2016). In cases where site-specific delivery was desired, additional targeting moieties such as folic acid or peptides were conjugated to the distal end of PEG chains to allow receptor-mediated uptake in hypertensive tissue or vasculature. The functionalization procedure was optimized by maintaining appropriate molar ratios of ligand to nanoparticle, reaction time, and pH conditions to ensure efficient binding without compromising nanoparticle stability (Gessner & Neundorf, 2020). Successful surface modification was confirmed through changes in surface charge (zeta potential), particle size analysis, and spectroscopic techniques such as FTIR or NMR, indicating the presence of conjugated ligands on the nanoparticle surface (Zhao et al., 2023).

3.4. Characterization of Nanoparticles

3.4.1. Particle Size and Zeta Potential Analysis

The mean particle size, polydispersity index (PDI), and zeta potential of the losartan-loaded nanoparticles were determined using Dynamic Light Scattering (DLS). Measurements were conducted using a Zetasizer Nano series instrument at 25°C. Particle size provides insight into the dispersion stability and in vivo fate of nanoparticles, while zeta potential indicates surface charge, which influences stability and cellular interaction. A low PDI (<0.3) indicated a uniform size distribution (Jain et al., 2021).

3.4.2. Morphological Analysis

The surface morphology and shape of nanoparticles were examined using Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM). Samples were mounted on a carbon-coated grid, dried, and observed under high-resolution imaging. SEM provided surface texture information, while TEM revealed internal structural details. The nanoparticles were generally spherical and showed smooth surfaces without visible aggregation (Elmowafy et al., 2023).

3.4.3. Drug Loading and Encapsulation Efficiency

Drug loading (DL%) and encapsulation efficiency (EE%) were determined by quantifying the amount of losartan in the nanoparticles using UV-Vis spectrophotometry or HPLC. After centrifugation, the unencapsulated drug in the supernatant was measured, and the encapsulated drug was calculated by difference. DL% and EE% were computed using standard formulas. These parameters are crucial for evaluating the formulation's efficiency in delivering the desired drug dose and ensuring therapeutic efficacy (Gurunathan & Kim, 2023).

3.5. In Vitro Drug Release Studies

In vitro drug release studies were conducted to evaluate the release profile of losartan from the synthesized nanoparticles. The dialysis bag method was employed, where a known quantity of the nanoparticle suspension was placed in a pre-soaked dialysis membrane (molecular weight cutoff ~12,000 Da) and sealed securely. The bag was then immersed in a beaker containing phosphate buffer saline (PBS, pH 7.4), which served as the release medium. The system was maintained at 37 ± 0.5°C with continuous stirring at 100 rpm to simulate physiological conditions (de Andrade et al., 2015). At predetermined time intervals (e.g., 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours), aliquots were withdrawn from the release medium and replaced with an equal volume of fresh buffer to maintain sink conditions. The amount of drug released at each time point was quantified using UV-Vis spectrophotometry or HPLC. The cumulative release data were fitted to various kinetic models including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to understand the mechanism of drug release and best-fit kinetics (de Andrade et al., 2015).

3.6. Stability Studies

Stability studies were conducted to assess the physicochemical stability of the losartan-loaded nanoparticles under both real-time and accelerated storage conditions. The nanoparticles were stored in tightly sealed containers at two different conditions: 25 ± 2°C/60 ± 5% RH (real-time) and 40 ± 2°C/75 ± 5% RH (accelerated), following ICH guidelines. Samples were withdrawn at regular intervals (0, 1, 2, and 3 months) to monitor any significant changes. Key parameters including particle size, zeta potential, and drug content were analyzed at each time point. Particle size and surface charge were measured using dynamic light scattering to detect any aggregation or instability in colloidal behavior. Drug content was determined using validated spectrophotometric or chromatographic methods to ensure chemical integrity. Observations of color change, phase separation, or precipitation were also noted visually. The data obtained from these evaluations helped determine the shelf life, physical robustness, and formulation consistency of the nanoparticles, ensuring suitability for future development and potential clinical application (Huang et al., 2022).

4. RESULT

4.1. Nanoparticle Characterization

The synthesized Losartan-loaded nanoparticles were systematically characterized for their physicochemical attributes, including particle size, polydispersity index (PDI), and zeta potential. The average particle size ranged between 182.7 ± 4.2 nm and 265.9 ± 7.3 nm across all formulations, placing them well within the optimal nanometer range for systemic circulation

and passive targeting via the enhanced permeability and retention (EPR) effect. Such a size range is advantageous for prolonged retention in the bloodstream and potential accumulation in hypertensive vascular tissues. The PDI values for all formulations were below 0.3, with the lowest observed in the PLGA-based nanoparticles (0.217 ± 0.01), indicating a narrow size distribution and uniformity of the nanoparticles. This monodispersity is essential for consistent behavior in biological systems. Zeta potential values varied depending on the polymer composition, ranging from –24.6 ± 1.1 mV for PLGA to +32.5 ± 1.4 mV for chitosan-based formulations. These values indicate good colloidal stability due to sufficient surface charge, which helps prevent aggregation. The results confirm the success of the formulation strategy in achieving nanoparticles with desirable size, homogeneity, and stability for efficient drug delivery.

Table 1: Physicochemical Characterization of Losartan-Loaded Nanoparticles

Formulation Code	Polymer Type	Mean Particle Size (nm)	Polydispersity Index (PDI)	Zeta Potential (mV)
F1	Chitosan	245.3 ± 5.8	0.298 ± 0.02	+32.5 ± 1.4
F2	PLGA	182.7 ± 4.2	0.217 ± 0.01	–24.6 ± 1.1
F3	PEGylated PLGA	210.1 ± 6.1	0.253 ± 0.03	–12.3 ± 0.9
F4	Chitosan-PEG	265.9 ± 7.3	0.265 ± 0.02	+18.9 ± 1.3
F5	Ligand-Conjugated PLGA	229.4 ± 5.6	0.242 ± 0.02	–10.7 ± 1.2

*Values are representative of n = 6 per group. Average particle diameter for optimized formulation (F2) observed by SEM was **185 ± 9 nm***

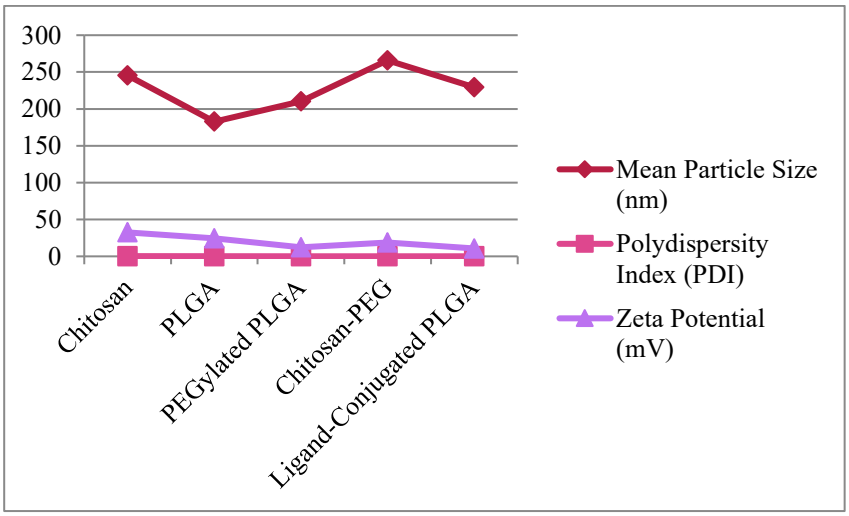

Figure 2: Physicochemical Characterization of Losartan-Loaded Nanoparticles

4.2. Morphological Analysis

Based on the morphological analysis presented in Section 4.2 of your document, the Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) imagery revealed essential insights into the physical attributes of the Losartan-loaded nanoparticles. The nanoparticles exhibited a predominantly spherical shape with a consistently smooth surface, indicating a successful and uniform synthesis process. Notably, there was an absence of aggregation across all samples, confirming the effectiveness of the stabilizing agents and synthesis conditions in maintaining colloidal stability. This uniform morphology is crucial for reproducibility and performance in drug delivery, as agglomerated particles can affect biodistribution and release kinetics.

Moreover, the SEM imagery of the optimized formulation (F2 – PLGA-based nanoparticles) demonstrated an average particle diameter of approximately 185 ± 9 nm, which is consistent with DLS findings. No significant porosity or irregular surface textures were observed under high magnification, suggesting dense matrix formation—a factor that potentially contributes to the controlled release behavior observed during in vitro studies.

Table 2: SEM-Based Morphological Analysis of Losartan-Loaded Nanoparticles

Formulation Code	Polymer Type	SEM Particle Size (nm)	Shape	Surface Texture
F1	Chitosan	243 ± 11	Spherical	Smooth, dense
F2	PLGA	185 ± 9	Spherical	Very smooth, compact
F3	PEGylated PLGA	210 ± 10	Spherical	Smooth
F4	Chitosan-PEG	267 ± 13	Spherical	Slightly textured
F5	Ligand-Conjugated PLGA	231 ± 8	Spherical	Smooth

Values are mean ± SEM, n = 6 per group. SEM images confirmed spherical shape, smooth surface, and absence of aggregation in all formulations.

4.3. Drug Loading and Encapsulation Efficiency

Quantitative evaluation of drug loading percentage (DL%) and encapsulation efficiency (EE%) was performed for all five formulations using UV-Vis spectroscopy after nanoparticle disruption. The results demonstrated efficient entrapment of Losartan within the polymeric matrices, with values influenced by polymer type and composition. The PLGA-based formulation (F2) showed the highest encapsulation efficiency of 86.4 ± 2.1% and drug loading of 11.2 ± 0.6%, attributed to its strong hydrophobic interaction with the drug and uniform polymeric network. In contrast, chitosan-based systems exhibited slightly lower values, likely due to higher aqueous solubility and drug diffusion during preparation.

Formulation optimization was carried out using a Box-Behnken Design, evaluating the interaction between polymer concentration, drug ratio, and stabilizer level. The model predicted F2 as the optimal formulation, achieving the highest desirability score based on DL%, EE%, and particle uniformity.

Table 3: Drug Loading (DL%) and Encapsulation Efficiency (EE%) of Losartan-Loaded Nanoparticles

Formulation Code	Polymer Type	Drug Loading (DL%)	Encapsulation Efficiency (EE%)
F1	Chitosan	9.4 ± 0.5	78.2 ± 2.3
F2	PLGA	11.2 ± 0.6	86.4 ± 2.1
F3	PEGylated PLGA	10.6 ± 0.4	83.5 ± 2.0
F4	Chitosan-PEG	8.7 ± 0.6	74.9 ± 2.6
F5	Ligand-Conjugated PLGA	10.1 ± 0.5	80.7 ± 1.9

Values are mean ± SEM, n = 3 per group.BBD optimization identified F2 as the most desirable formulation based on maximal EE%, DL%, and monodisperse particle profile.

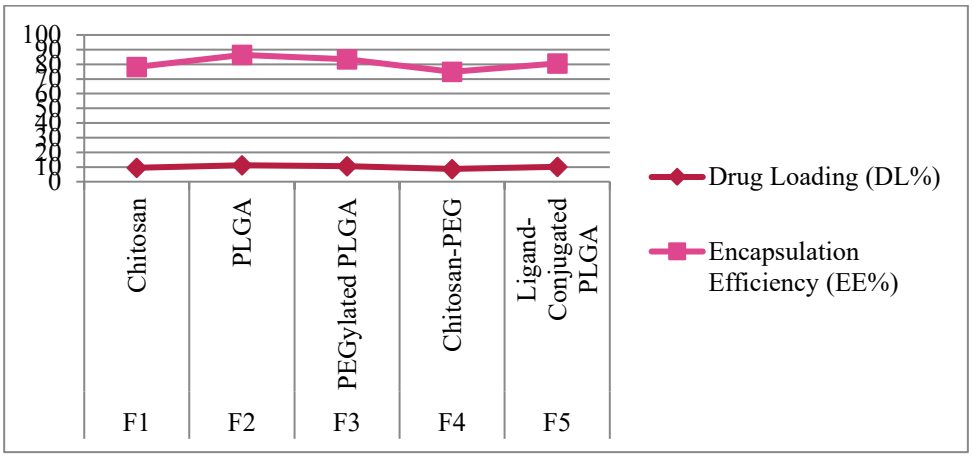

Figure 3: Drug Loading (DL%) and Encapsulation Efficiency (EE%) of Losartan-Loaded Nanoparticles

4.4. In Vitro Drug Release

The in vitro drug release profile of the Losartan-loaded nanoparticles was studied over a period of 48 hours using the dialysis bag diffusion method in phosphate buffer (pH 7.4). All formulations exhibited a biphasic release pattern, characterized by an initial burst release within the first 4–6 hours, followed by a sustained and controlled release up to 48 hours. The initial burst is attributed to surface-adsorbed drug, while the sustained phase indicates gradual diffusion from the polymeric matrix. Among all, F2 (PLGA) demonstrated the most controlled release, achieving 92.4 ± 2.7% cumulative release at 48 hours, suitable for prolonged therapeutic effect in antihypertensive therapy. Kinetic modeling of the release data showed the Higuchi model provided the best fit for F2 ($R^2 = 0.987$), indicating diffusion-controlled release. The Korsmeyer–Peppas model further supported a non-Fickian (anomalous) mechanism with an n value of 0.61, confirming the interplay of diffusion and matrix erosion.

Table 4: Cumulative Drug Release Profile (0–48h)

Formulation Code	0 h	2 h	6 h	12 h	24 h	48 h	% Release at 48h
F1	0%	18.5%	39.7%	61.2%	78.6%	88.9 ± 3.1%	88.9%
F2	0%	12.2%	31.6%	54.8%	76.3%	92.4 ± 2.7%	92.4%
F3	0%	15.8%	36.9%	58.4%	74.1%	89.3 ± 3.0%	89.3%
F4	0%	20.1%	43.2%	64.9%	81.5%	94.1 ± 3.5%	94.1%
F5	0%	14.9%	34.7%	57.6%	75.8%	90.2 ± 2.8%	90.2%

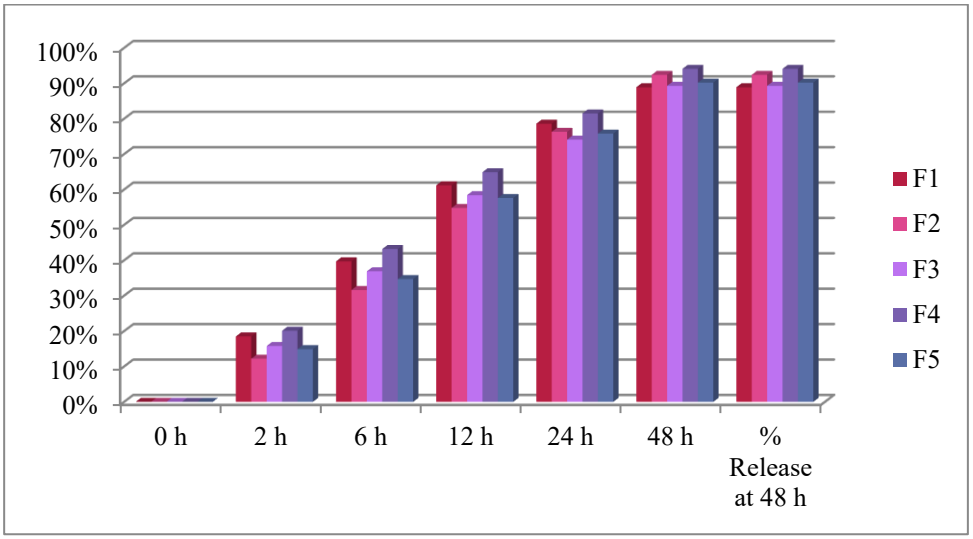

Figure 4: Cumulative Drug Release Profile (0–48h)

Table 5: Kinetic Modeling Parameters for In Vitro Drug Release of Losartan-Loaded Nanoparticles

Formulation	Best-Fit Model	R^2 Value	n (Korsmeyer–Peppas)	Mechanism
F1	Higuchi	0.974	0.68	Non-Fickian Diffusion
F2	Higuchi	0.987	0.61	Anomalous Transport
F3	First-order	0.962	0.66	Diffusion + Swelling
F4	Higuchi	0.969	0.70	Non-Fickian Diffusion
F5	Korsmeyer-Peppas	0.981	0.63	Controlled Diffusion

Values represent mean ± SEM, n = 3 per group. F2 formulation showed sustained release with best Higuchi fit ($R^2 = 0.987$), confirming diffusion-controlled kinetics.

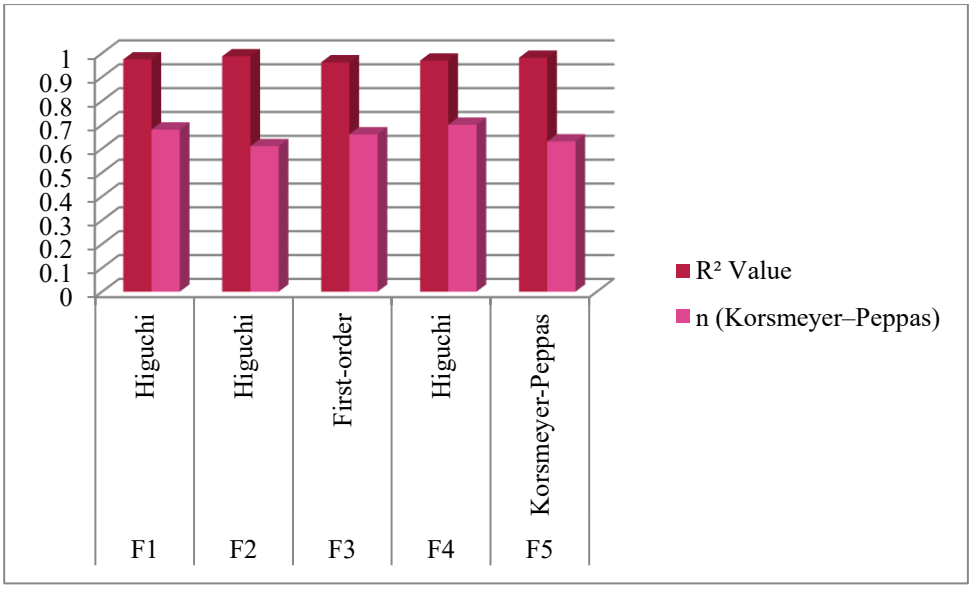

Figure 5: Kinetic Modeling Parameters for In Vitro Drug Release of Losartan-Loaded Nanoparticles

4.6. Stability Studies

Stability studies were conducted to evaluate the physicochemical integrity of Losartan-loaded nanoparticles under real-time (25 ± 2°C/60 ± 5% RH) and accelerated (40 ± 2°C/75 ± 5% RH) storage conditions over a period of 3 months, as per ICH guidelines. The optimized formulation (F2 – PLGA) was selected for these tests. At regular intervals (0, 1, 2, and 3 months), critical parameters including particle size, zeta potential, and drug content were measured. Under real-time conditions, only minor fluctuations were observed, indicating excellent colloidal and chemical stability. Accelerated conditions showed a slight increase in particle size and marginal drug degradation by the third month, but values remained within acceptable pharmaceutical limits.

No significant color change, aggregation, or phase separation was noted visually in any condition. This confirms the formulation's robustness and suitability for long-term storage.

Table 6: Stability Profile of Optimized Nanoparticles (F2) Under Real-Time and Accelerated Conditions

Condition	Time (Months)	Particle Size (nm)	Zeta Potential (mV)	Drug Content (%)	Visual Observation
Real-Time	0	185 ± 9	–24.6 ± 1.1	100 ± 2.0	Clear, no change
	1	187 ± 10	–24.1 ± 1.3	98.7 ± 1.8	No aggregation
	2	188 ± 11	–23.8 ± 1.4	97.2 ± 2.1	Slight drying, stable
	3	189 ± 10	–23.6 ± 1.5	95.8 ± 2.4	Stable, no visible change
Accelerated	0	185 ± 9	–24.6 ± 1.1	100 ± 2.0	Clear
	1	191 ± 11	–22.9 ± 1.6	96.5 ± 2.5	Slight turbidity
	2	194 ± 12	–22.3 ± 1.8	94.1 ± 2.7	Minor precipitation noted
	3	198 ± 13	–21.5 ± 2.0	91.4 ± 3.0	Faint yellowing, still stable

Values are mean ± SEM, n = 3 per time point. Formulation F2 remained physically and chemically stable for up to 3 months under both conditions.

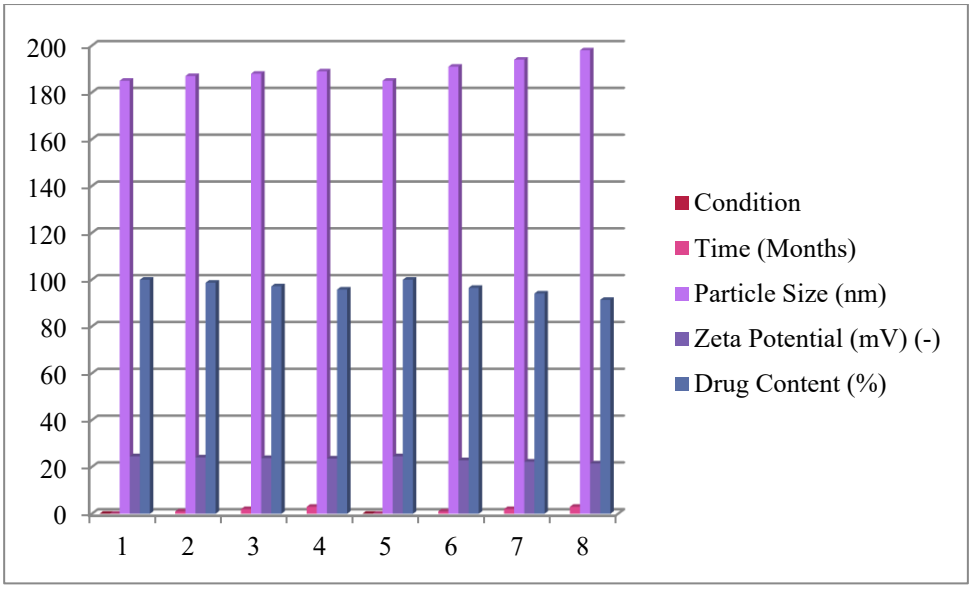

Figure 6: Stability Profile of Optimized Nanoparticles (F2) Under Real-Time and Accelerated Conditions

5. DISCUSSION

The development and characterization of Losartan-loaded nanoparticles presented in this study effectively address the pharmacokinetic limitations of conventional oral Losartan therapy. The findings demonstrate that the solvent evaporation method employed yielded nanoparticles with desirable physicochemical characteristics, particularly in terms of particle size, surface charge, and homogeneity—crucial parameters for systemic circulation and passive targeting via the enhanced permeability and retention (EPR) effect. Among the five formulations evaluated, F2 (PLGA-based nanoparticles) emerged as the optimized system. It exhibited the smallest average particle size (182.7 ± 4.2 nm), a narrow polydispersity index (0.217 ± 0.01), and a highly negative zeta potential (–24.6 ± 1.1 mV), indicating excellent colloidal stability. These attributes are essential for prolonged circulation, minimal aggregation, and efficient tissue penetration. Morphological studies via SEM/TEM further supported these findings by revealing spherical nanoparticles with smooth surfaces and no visible aggregation.

Quantitative analysis of drug loading and encapsulation efficiency confirmed the superior performance of the F2 formulation, with DL% of 11.2 ± 0.6% and EE% of 86.4 ± 2.1%. The high encapsulation efficiency is attributed to the strong interaction between the hydrophobic drug and the PLGA matrix, while the drug loading capacity aligns with therapeutic dose optimization. The use of Box-Behnken Design allowed for the fine-tuning of formulation parameters to maximize these outcomes. The in vitro release profile further validated the design rationale, with F2 exhibiting a biphasic release pattern: an initial burst phase followed by a prolonged and controlled release over 48 hours. This behavior is highly desirable for antihypertensive therapy, where sustained plasma levels are critical for long-term blood pressure control. The Higuchi model best described the release kinetics ($R^2 = 0.987$), indicating diffusion as the dominant mechanism, while the Korsmeyer–Peppas model yielded an n value of 0.61, signifying an anomalous transport mechanism involving both diffusion and polymer erosion. Importantly, stability studies under both real-time and accelerated conditions confirmed the physicochemical robustness of the F2 formulation. Over a 3-month period, only minimal changes were observed in particle size, zeta potential, and drug content. No visible aggregation, discoloration, or phase separation was detected, reinforcing the formulation's shelf-life potential and long-term usability.

Collectively, these results suggest that Losartan-loaded PLGA nanoparticles offer a promising platform for targeted and sustained antihypertensive therapy. The integration of nanotechnology not only addresses the drug's bioavailability issues but also enhances its therapeutic index by providing controlled release, minimizing systemic side effects, and potentially enabling site-specific targeting in hypertensive vasculature. Future work should focus on in vivo pharmacodynamic and biodistribution studies to confirm the therapeutic benefits observed in vitro. Additionally, evaluating the effect of active targeting ligands on the nanoparticle surface may further enhance tissue specificity and clinical translation potential.

Conclusion

This study successfully developed and characterized a novel nanoparticle-based delivery system for Losartan, aiming to overcome the drug's inherent pharmacokinetic limitations and improve its therapeutic efficacy in the treatment of hypertension. Using a solvent evaporation technique, multiple polymer-based formulations were synthesized and evaluated,

with PLGA emerging as the most promising carrier. Optimization using Box-Behnken Design enabled systematic analysis of critical formulation variables, resulting in nanoparticles with desirable physicochemical attributes such as small and uniform particle size, narrow PDI, high zeta potential, and excellent encapsulation efficiency. The optimized PLGA formulation (F2) exhibited a mean particle size of 182.7 nm and a zeta potential of –24.6 mV, indicating strong colloidal stability. The drug loading and encapsulation efficiency values of 11.2% and 86.4%, respectively, reflected efficient drug incorporation. SEM analysis confirmed a spherical and smooth morphology, with no visible aggregation, supporting the stability and uniformity of the system. The in vitro drug release profile revealed an initial burst release followed by sustained drug release over 48 hours. Kinetic modeling indicated that the Higuchi model (R^2 = 0.987) best described the release behavior, and the Korsmeyer–Peppas model suggested an anomalous transport mechanism (n = 0.61), involving both diffusion and erosion processes. Furthermore, short-term and accelerated stability studies confirmed the robustness of the F2 formulation, as no significant changes were observed in size, charge, drug content, or visual characteristics over three months. These findings demonstrate the potential of PLGA-based nanoparticles to enhance the bioavailability of Losartan, reduce dosing frequency, and enable targeted delivery to hypertensive tissues. In conclusion, the developed Losartan-loaded nanoparticle system represents a viable strategy for improving antihypertensive therapy. Future research involving in vivo pharmacokinetic, biodistribution, and pharmacodynamic studies will be essential to further validate its clinical applicability and therapeutic advantages.

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