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Original Article

Development of Azilsartan Nanoparticles via Hydrolysis for Enhanced Drug Delivery

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ABSTRACT

Background: Hypertension is a major global health concern and a primary risk factor for cardiovascular morbidity and mortality. Azilsartan medoxomil, a novel angiotensin II receptor blocker, is effective in blood pressure reduction but suffers from poor aqueous solubility and variable oral bioavailability. Nanoparticle-based delivery systems, particularly using chitosan, offer a strategy to overcome these limitations by enhancing solubility, dissolution, and stability. **Materials and Methods:** Azilsartan medoxomil nanoparticles (AZL-NP) were prepared using the ionic gelation technique with chitosan and sodium tripolyphosphate as cross-linkers. Preformulation studies included solubility testing, FTIR compatibility, and melting point determination. Nanoparticles were characterized for particle size, Polydispersity Index (PDI), zeta potential, and drug content. Morphological evaluation was conducted using Atomic Force Microscopy (AFM) and Scanning Electron Microscopy (SEM), while X-ray Diffraction (XRD) was performed for structural analysis. Lyophilized nanoparticles were compressed into tablets and subjected to physicochemical and *in vitro* release studies. **Results and Discussion:** Optimized formulation showed a mean particle size of 479.4 nm, PDI of 0.239, and zeta potential of +34.2 Mv, confirming good stability. AFM and SEM revealed nanoparticles with irregular to semi-spherical morphology, and XRD indicated partial crystallinity. Formulated tablets complied with pharmacopeia limits for hardness, friability, and disintegration. *In vitro* dissolution studies demonstrated rapid and enhanced release, with 95.85% of drug released within 60 min, compared to conventional tablets. Release kinetics followed first-order and korsmeyer-peppas models, indicating non-fickian diffusion. **Conclusion:** Azilsartan medoxomil loaded chitosan nanoparticles were successfully developed and optimized, showing improved solubility, dissolution rate, and drug release compared to conventional formulations. The nanoparticle-based system demonstrates significant potential to enhance the oral bioavailability and therapeutic efficacy of Azilsartan in hypertension management.

Keywords: Azilsartanmedoxomil, Chitosan nanoparticles, Drug delivery, Hypertension, Ionic gelation, Solubility enhancement.

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INTRODUCTION

Hypertension is one of the most prevalent chronic diseases worldwide and represents the leading modifiable risk factor for cardiovascular morbidity and mortality (Wang *et al.*, 2021). Despite the availability of multiple antihypertensive agents, control rates remain suboptimal, and hypertension continues to contribute substantially to global disease burden, accounting for nearly 9.4 million deaths annually (Lou *et al.*, 2023; Wang *et al.*, 2021). Current international guidelines emphasize the importance of effective blood pressure control to reduce the risk of target organ damage and cardiovascular events. Angiotensin II Receptor Blockers (ARB) are widely recommended as first-line therapy, particularly for patients with comorbidities such as diabetes, renal dysfunction, and heart failure. Azilsartan medoxomil (AZL-M), a novel ARB, has been shown to provide superior and sustained blood pressure reduction compared with other agents in its class (Baker *et al.*, 2012). A recent systematic review and meta-analysis confirmed its efficacy and safety, demonstrating significant reductions in both systolic and diastolic blood pressure without increasing the risk of adverse events (Zhu *et al.*, 2024). Among the various antihypertensive agents, Azilsartan Medoxomil (AZL-M), a prodrug of azilsartan and a selective angiotensin II type 1 receptor blocker, is widely used. However, its therapeutic efficacy is often compromised by its poor aqueous solubility (0.0037 mg/mL) and variable oral bioavailability (Chopra *et al.*, 2020). Nanoparticle drug delivery systems, particularly those based on biodegradable polymers like chitosan, have gained significant attention due to their ability to enhance solubility, improve permeability, and sustain drug release (Chopra *et al.*, 2019; Lou *et al.*, 2023). Chitosan is a

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natural cationic polysaccharide with favorable biocompatibility, biodegradability, and mucoadhesive properties, making it suitable for oral and nasal delivery routes (Chakraborty *et al.*, 2025; Hoang *et al.*, 2022). Among the available fabrication methods, the ionic gelation technique using sodium Tripolyphosphate (TPP) as a cross-linker is simple, non-toxic, and avoids the use of harmful organic solvents. Recent studies have demonstrated that Chitosan Nanoparticles (CH-NP) not only enhance drug solubility but also provide controlled release, improved pharmacokinetics, and potential site-specific delivery chitosan nano particles. For poorly water-soluble drugs like azilsartan medoxomil, encapsulation into CH-NP can significantly improve dissolution and bioavailability, ultimately leading to enhanced therapeutic efficacy (Hoang *et al.*, 2022; Jain *et al.*, 2023). Azilsartan medoxomil belongs to Biopharmaceutical Classification System (BCS) Class II, characterized by poor aqueous solubility and high permeability, which limits its dissolution and oral bioavailability. The present work aims to develop and evaluate azilsartan medoxomil-loaded chitosan nanoparticles using the ionic gelation method. The study focuses on improving solubility, dissolution rate, and overall bioavailability of the drug, with a view to overcoming its biopharmaceutical limitations and providing an efficient alternative drug delivery system (De Pinho Neves *et al.*, 2014; Mohamed *et al.*, 2025).

MATERIALS AND METHODS

Materials

Azilsartan medoxomil, chitosan, tripolyphosphate, hydroxypropyl methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, mannitol, talc, Starch glycolate, magnesium stearate was used. Unless otherwise stated all chemicals and solvents are used in analytical grade.

Methods

Preformulation Studies

The AZL stock solution was prepared and analysed by using a double beam UV visible spectrometer (UV 1650 PC Shimadzu). The melting points of AZL were determined by the capillary method. Using a digital melting point instrument (Selec TC 303). The solubility of AZL was evaluated in various solvents including water and methanol by saturation solubility method. Drug and physical mixture compatibility were analysed through FTIR Spectrophotometer (Das *et al.*, 2024).

Formulation and Optimization Process

Formulation of nanoparticles by ionic gelation technique and Low, medium, high molecular weight chitosan was dissolved in 1% acetic acid solution and AZL dissolved in methanol, and tripolyphosphate in water with ratio 7:3:3 for preparation of nanoparticles. Chitosan solution set on magnetic stirrer under stirring condition and add AZL solution drop by drop to chitosan solution. Then after opalescent suspension appeared then cross link with the TPP solution. The mixture was homogenized at 7000 rpm at 5mins prior to lyophilization (Van *et al.*, 2023).

Evaluation of Azilsartan Medoxomil Nanoparticles

The average particle size, PDI and zeta potential were measured by using dynamic light scattering principle of Malvern zeta seizer (Malvern Instrument, Malvern, UK). The samples were diluted with water and placed in the disposable cuvvete and electrophoretic cell (Jassem *et al.*, 2017; Madan *et al.*, 2021).

Drug Content

The freeze-dried powder 10 mg would be taken in standard measuring flask and diluted with solvent which solubilize the drug (methanol for Azilsartan medoxomil). Further the stock solution is diluted with same solvent and measured in UV-visible spectroscopy to evaluate the concentration (Das *et al.*, 2024; Tamboli *et al.*, 2020).

Morphological Study by AFM

The surface morphology of drug entrapped nanoparticle was determined using Atomic Force Microscopy (AFM) (Ntegra-Nt-Mdt, RUSSIA). Place the sample securely onto the AFM stage or holder. The sample should be clean and flat to ensure accurate measurements, after mounting Perform system calibration, including the calibration of the AFM cantilever's spring constant, optical lever sensitivity, and other relevant parameters. Use the AFM software to position the AFM tip above the sample at a safe distance. Initiate the scanning process, allowing the AFM tip to raster across the sample surface while measuring the surface topography and collecting data (Jassem *et al.*, 2017).

Morphological Study by SEM

Structural morphology of AZLNPs with CH:AZL:TPP weight ratio 7:3:3 was carried out using Scanning Electron Microscopy (SEM) instrument (ZEISS EVO 18, GERMANY). SEM is a constructive characterization technique that provides information on the surface features and morphology (particles' shape, size, and arrangement) of the sample. It is comprised of a thermionic gun as an electron source along with other components (Angeli *et al.*, 2013).

Structural Characterization by XRD

To determine the nature of AZL NPs, powder X-ray Diffraction (PXRD) analysis was performed using an Empyrean Series III diffractometer (Malvern Panalytical, UK) with Ni-filtered Cu-Kα radiation. Samples were scanned at 2θ angles ranging from 5° to 120° at room temperature in continuous mode with a step size of 0.02°/s. Changes in the diffraction peak positions of AZL were analysed to evaluate alterations in the crystal structure resulting from nanoparticle formation (Jassem *et al.*, 2017).

Characterization of AZL-NP Tablets

The tablets were prepared (Table 1) and common quality assessment tests of tablets were conducted included weight variation, thickness and diameter, friability, disintegration test, hardness, content uniformity analysis (Jain *et al.*, 2023; De Catrina *et al.*, 2012).

In vitro Drug Release Studies

Dissolution test was performed using USP apparatus 2 in dissolution testing apparatus (Labindia Instruments Pvt. Ltd., India). Azilsartan medoxomil nanoparticles using phosphate buffer (pH 6.8 and 7.4) dissolution medium of 900 mL, maintained at 37.0±0.5°C. The paddle rotation speed was set at 75 rpm. For each formulation, six tablets were tested. At predetermined time points, 5 mL samples were withdrawn, and the samples were determined using a UV spectrophotometer (Fan et al., 2012; Madhan *et al.*, 2023).

In vitro Drug Release Kinetics

Dissolution data of dosage form were subjected to kinetic modeling using various mathematical models, namely zero-order, first-order, higuchi, and korsmeyer peppas (Angeli *et al.*, 2013; Ma *et al.,* 2017).

Statistical Analysis

The kinetic modeling was performed using DD solver to analyze the order of drug release and type of diffusion from tablet dosage form.

Ethical Statement

Ethical approval was not required as the study is primarily *in vitro* physicochemical work.

Financial Support and Sponsorship Statement

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AUTHOR CONTRIBUTIONS

Both authors had contributed in research planning, work done and interpretation of data, scientific content writing. Communication of paper to the journal is covered by Subramanian somaskanthan.

RESULTS

Preformulation Studies UV analysis was performed for AZL has observed maximum lambda max followed by plotted standard curve. The melting point of AZL was found to be 214°C determined using capillary tube method. The solubility studies observed AZL was soluble in methanol, freely soluble and very slightly soluble in water. FTIR studies conformed no physical interaction occur within the drugs and excipient mixture.

Evaluation of AZL Nanoparticles Low molecular weight showed higher positive zeta potential, lower size, and best PDI. Low molecular weight CH-NP is stable while medium molecular weight CH-NP unstable after 30 mins of preparation by deviating in the value of size, PDI and zeta potential while measuring in zetasizer.

Drug ContentDrug content for azilsartan medoxomil was 0.23 mg in 1 mg of nanoparticles.

Conversion to Solid ParticlesThe drug loaded nanoparticle is intended to freeze to -80°C and the particles are transferred to freeze drier to sublimate the solvent for 5 days. The obtained lyophilizationproducts are characterized and loaded to tablet (Table 1).

Morphological Study by AFM Formulated nanoparticles were analysed for AFM microscopy showed nanoparticles was 162.943nm for 65536 nanoparticles analysed. Maximum size was 265.716nm, minimum size was 0 nm, Average Roughness was 26.8421nm.

Morphology Study by SEM Further, freeze dried formulated nanoparticles are analysed by the SEM analysis. It revealed that the chitosan nanoparticles exhibited irregular to semi-spherical morphology. Observed size range was approximately 325 to 788 nm (Figure 1).

Structural Characterization by XRDXRD analysis of formulated nanoparticles was performed and observed in 10 to 90° (2θ). A diffuse, broad peak is observed between 10° and 30° (2θ) as shown (Figure 2).

Characterization of AZL-NP Tablet The characterization of AZL-NP tablets, including weight variation, thickness and diameter, friability, hardness, disintegration time, and content uniformity, demonstrated that all parameters fall within their respective ideal ranges (Table 2).

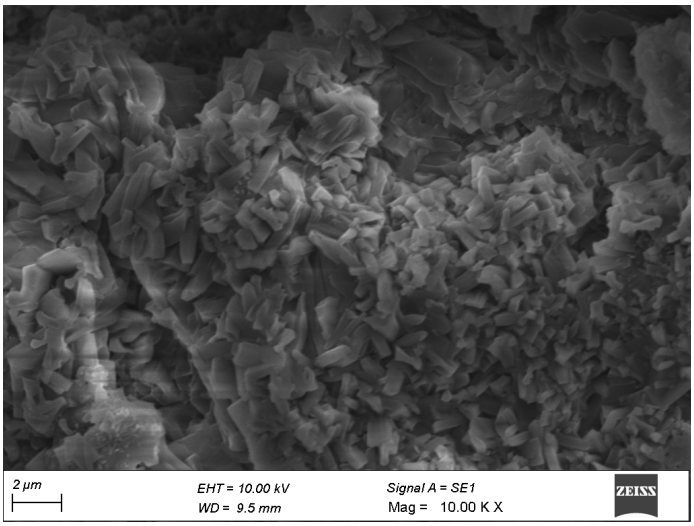

Figure 1: SEM image of azilsartan medoxomil nanoparticles.

In vitro Drug Release Studies Azilsartan medoxomil showed an extended release, with 1.17% of the drug released at 5 min and 95.85% within 60 min. These findings suggest that the release profiles of the prepared Azilsartan medoxomil tablet release were extended drug release.

In vitro Drug Release KineticsUsing DD Solver software used for *in vitro* drug release kinetics. The release kinetics of Azilsartan medoxomil nanoparticles tablet and Azilsartan medoxomil conventional tablets both, followed first-order release (0.8819±0.009 and 0.918±0.014 for AZL and AZL_NP respectively) and korsmeyer peppas (0.522±0.01 and 0.549±0.006 for AZL and AZL_NP respectively) model confirms a non-fickian diffusion mechanism of drug release.

DISCUSSION

In this study low molecular weight chitosan was taken in the ratio of CH: AZL: TPP as (0.1%) 7:3:3 for formulation of nanoparticles with drug (Table 3). Drug content is 100% when compared to theoretical drug content. AFM morphology of AZL-NP with 2 D image (Figure 3) indicates that the particles are irregular shape. XRD sharp peak represents crystalline nature of AZL-NP. Characterization of AZL-NP tablets are compiled

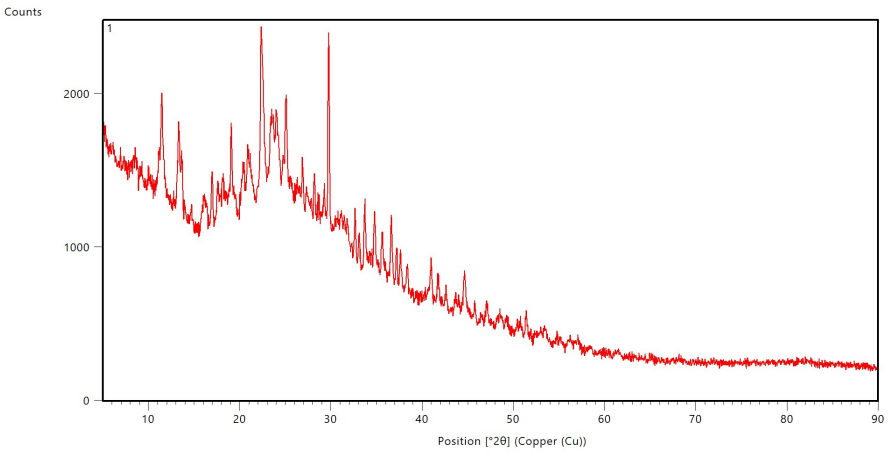

Figure 2: XRD image of azilsartan medoxomil nanoparticles.

Table 1: Composition of AZL tablets.

Sl. No.	Ingredients	Weight (in mg)
1.	AZL NP	173.91
2.	HPMC	12
3.	MCC	75
4.	Polyvinyl pyolidone	15
5.	Mannitol	87
6.	Talc	2
7.	Starch glycolate	15
8.	Magnesium stearate	6

Table 2: Summary of characterization of AZL tablet data.

Evaluation parameter	Observed results
Weight variation test	385.9±2.57 mg
Thickness	4.2±0.075 mm
Diameter	6.9±0.073 mm
Friability test	0.25±0.078%
Hardness test	62±2.85 N
Disintegration test	14.9±0.589 min
Content uniformity	95.1±0.91%

Table 3: Different molecular weight CH NPs.

Items	Size	PDI	Zeta Potential
Lower	479.4 nm	0.239	34.2 mv
Medium	NA	NA	NA

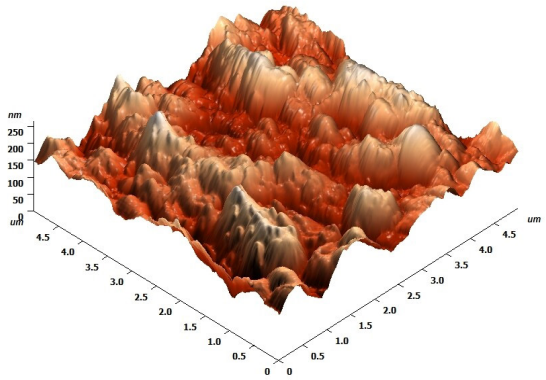

Figure 3: AFM image of Azilsartan nanoparticle 2D image of AFM.

with IP standard. AZl-NP are released in extended manner when compared with conventional AZL tablets. Release kinetics also proves the extended drug release with non-fickian diffusion of AZL from AZL-NP tablet.

CONCLUSION

Azilsartan medoxomil, a poorly water-soluble BCS class II antihypertensive drug, was successfully formulated into stable chitosan-based nanoparticles to overcome its solubility limitations. Optimized nanoparticles demonstrated favorable physicochemical characteristics, with a mean particle size of 479.4 nm, a PDI of 0.239, and a zeta potential of +34.2 mV, confirming good stability. Morphological analyses (AFM and SEM) revealed spherical to semi-spherical particles with uniform distribution, while XRD confirmed partial crystallinity, supporting improved dissolution potential. Lyophilized AZL-NP was effectively converted into tablets that complied with pharmacopeial standards for hardness, friability, and disintegration. *In vitro* dissolution studies indicated markedly improved drug release compared with conventional tablets, including an 11-fold increase in solubility within 10 min and an 18% enhancement in dissolution rate after 1 hr. Drug release kinetics followed first-order and korsmeyer-peppas models, suggesting a non-fickian diffusion mechanism. Overall, the developed AZL-NP based formulation demonstrated significant improvements in solubility and dissolution, indicating strong potential to enhance oral bioavailability and therapeutic efficacy in the management of hypertension.

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ABBREVIATIONS

AZL: Azilsartan medoxomil; **AZL-NP:** Azilsartan medoxomil nanoparticles; **ARB:** Angiotensin II receptor blockers; **TPP:** Sodium tripolyphosphate; **FTIR:** Fourier Transform Infrared; **PDI:** Poly dispersity index; **AFM:** Atomic force microscopy; **SEM:** Scanning electron microscopy; **XRD:** X-ray diffraction; **CH:** Chitosan; **CH-NP:** Chitosan nanoparticle; **BCS:** Biopharmaceutical Classification System; **UV:** Ultraviolet; **IP:** Indian Pharmacopeia; **HPMC:** Hydroxypropyl methylcellulose; **MCC:** Microcrystalline cellulose; **PVP:** Polyvinyl pyrrolidone; **Talc:** Talcum.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

AZL-NP was prepared by inoicgelation technique with better nanosize, PDI and zeta potential. Further it was confirmed by AFM, SEM and XRD analysis. The prepared nanoparticles were converted as unit solid dosage form of tablet. The tablets were confirmed for their quality by various parameters and confirmed its increase in dissolution rate by 18% by 1 hr by non-fickian diffusion from the tablet with first order release kinetics.

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