ISSN 1998 – 409X

RESEARCH ARTICLE

Comparative Evaluation of Polyethylene Glycol 4000-Based Solid Dispersions and D-α-Tocopheryl Polyethylene Glycol Succinate Micellar Nanocarriers for Solubility Enhancement of Azelnidipine

Srushti Shah[1], Vandana Patel[2]

[1]Department of Quality Assurance, Faculty of Pharmacy, Parul Institute of Pharmaceutical Education and Research, Parul University, Vadodara, Gujarat, India, [2]Department of Quality Assurance, Faculty of Pharmacy, Parul College of Pharmacy, Parul University, Vadodara, Gujarat, India

Abstract

Objectives: The present study aimed to comparatively evaluate two distinct formulation approaches, namely polyethylene glycol 4000 (PEG4000)-based solid dispersions and D-α-tocopheryl polyethylene glycol succinate (TPGS) micellar nanocarriers, for improving the solubility and dissolution characteristics of azelnidipine (AZP), a poorly water-soluble antihypertensive drug. **Materials and Methods**: Data pertaining to formulation methodology, physicochemical characterization, particle size, dissolution profile, and drug encapsulation efficiency were extracted from previously published investigations involving PEG4000 solid dispersions and TPGS micellar systems of AZP. Comparative assessment was performed based on formulation attributes, mechanism of solubility enhancement, release behavior, and pharmaceutical applicability. **Results**: PEG4000 solid dispersions prepared by solvent evaporation significantly improved dissolution performance, exhibiting approximately 95% cumulative drug release within 30 min. TPGS micellar systems prepared through self-assembly generated nanosized carriers (10–20 nm) with entrapment efficiencies approaching 86% and demonstrated sustained release characteristics. PEG4000 systems improved dissolution primarily through amorphization and enhanced wettability, whereas TPGS micelles enhanced aqueous solubility by nanoscale encapsulation within hydrophobic cores. **Conclusion**: Both formulation strategies effectively enhanced the pharmaceutical performance of AZP. PEG4000 solid dispersions were found suitable for immediate-release applications owing to rapid dissolution, whereas TPGS micelles represented an advanced nanocarrier platform offering sustained release and improved colloidal stability.

Key words: Azelnidipine, D-α-tocopheryl polyethylene glycol succinate micelles, nanocarriers, polyethylene glycol 4000, solid dispersion, solubility enhancement

INTRODUCTION

Poor aqueous solubility remains one of the foremost challenges encountered during pharmaceutical product development. It has been estimated that approximately 40–70% of newly discovered chemical entities exhibit poor aqueous solubility, leading to inadequate dissolution in gastrointestinal fluids and consequently poor oral bioavailability.[1-3] Since oral administration is the most preferred route for drug delivery due to patient convenience and compliance, formulation strategies capable of improving solubility and dissolution characteristics are of immense pharmaceutical importance.[4]

According to the biopharmaceutical classification system (BCS), drug molecules are classified into four categories based on their aqueous solubility and intestinal permeability characteristics. BCS Class II drugs possess high membrane permeability but poor aqueous solubility, resulting in dissolution-limited absorption following oral administration.

Address for correspondence:
Srushti Shah, Parul Institute of Pharmaceutical Education and Research, Parul University, Vadodara, Gujarat, India.
E-mail: srushtishah1993@gmail.com

Received: 16-07-2026
Revised: 26-08-2026
Accepted: 07-09-2026

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For such drugs, enhancement of dissolution characteristics represents a critical requirement for improving systemic bioavailability and therapeutic performance.[5,6]

Azelnidipine (AZP) is a third-generation dihydropyridine calcium channel blocker extensively employed in the management of hypertension.[7,8] Unlike conventional calcium channel blockers, AZP exhibits prolonged antihypertensive action with reduced reflex tachycardia, improved cardiovascular protection, and favorable patient tolerability.[8-10] However, despite its potent pharmacological activity, AZP demonstrates poor aqueous solubility and low oral bioavailability, thereby limiting its clinical effectiveness.[11-13]

The intrinsic aqueous solubility of AZP has been reported to be extremely low, categorizing it as a BCS Class II drug.[11,12] Following oral administration, the rate and extent of AZP absorption are primarily governed by its dissolution behavior within gastrointestinal fluids.[14] Incomplete dissolution frequently leads to variable absorption, inconsistent plasma concentrations, and reduced therapeutic efficacy. Consequently, several formulation approaches have been investigated to overcome these limitations.[15]

Numerous pharmaceutical strategies have been proposed for enhancing the solubility of poorly water-soluble drugs, including particle size reduction, crystal engineering, inclusion complexation, salt formation, lipid-based systems, solid dispersions, nanosuspensions, self-emulsifying systems, polymeric nanoparticles, and micellar drug delivery systems.[15-18] Among these approaches, solid dispersion technology has emerged as one of the simplest and most industrially feasible methods for enhancing dissolution.

Solid dispersion systems involve molecular dispersion of poorly soluble drugs within hydrophilic polymer matrices.[13,19] Such systems improve dissolution through multiple mechanisms, including reduction in crystallinity, transformation of crystalline drug into amorphous form, enhanced wettability, improved dispersibility, and increased effective surface area. Hydrophilic carriers including polyethylene glycols (PEGs), polyvinylpyrrolidone, hydroxypropyl methylcellulose, and poloxamers have been extensively investigated for solid dispersion preparation.[5,12]

PEG 4000 has gained substantial attention owing to its excellent aqueous solubility, low toxicity, pharmaceutical acceptability, ease of processing, and capability to improve wettability of hydrophobic drugs.[14,15,20] PEG4000-based solid dispersions have demonstrated significant enhancement in dissolution profiles of several poorly soluble drug molecules. The solvent evaporation technique remains one of the most commonly employed approaches for preparing PEG4000 solid dispersions due to its simplicity and ability to achieve uniform drug distribution.[16,17]

Recent advancements in pharmaceutical nanotechnology have introduced novel nanocarrier systems for improving solubility and oral bioavailability.[19,21] Polymeric micelles represent one such promising platform capable of solubilizing poorly water-soluble drugs through spontaneous self-assembly of amphiphilic molecules in aqueous environments.[6,7]

D-α-Tocopheryl polyethylene glycol succinate (TPGS), a water-soluble derivative of natural Vitamin E, has emerged as a versatile pharmaceutical excipient owing to its amphiphilic structure. TPGS possesses a hydrophobic Vitamin E moiety and a hydrophilic PEG chain, enabling spontaneous formation of nanosized micelles above its critical micelle concentration (CMC). The hydrophobic core of TPGS micelles serves as a reservoir for encapsulation of poorly soluble drugs, thereby markedly increasing apparent aqueous solubility.[11,14]

In addition to solubilization, TPGS offers several unique advantages, including excellent biocompatibility, low toxicity, inhibition of P-glycoprotein-mediated efflux, enhancement of intestinal permeability, improved stability, and potential for sustained drug release. Consequently, TPGS micellar systems have gained considerable interest as advanced nanocarriers for oral delivery of poorly soluble therapeutic agents.

Although both PEG4000-based solid dispersions and TPGS micellar systems have independently demonstrated promising outcomes for improving the dissolution characteristics of AZP, direct comparative analysis between these two formulation strategies remains limited. Comparative evaluation is important because both systems employ fundamentally different mechanisms for enhancing drug solubility. While PEG4000 solid dispersions rely primarily upon drug amorphization and improved wettability, TPGS micelles utilize nanoscale encapsulation and micellar solubilization mechanisms.[12,13]

Furthermore, understanding the relative advantages and limitations associated with each approach is essential for rational formulation selection during pharmaceutical product development. Conventional solid dispersions offer simplicity, low manufacturing cost, and excellent scale-up feasibility, whereas nanocarrier systems provide enhanced stability, sustained release characteristics, and potential improvement in oral bioavailability.[5,11,14]

Therefore, the present study was undertaken to comparatively evaluate PEG4000-based solid dispersions and TPGS micellar nanocarriers for enhancement of AZP solubility. Comparative assessment was performed with respect to formulation methodology, physicochemical characteristics, mechanisms of solubility enhancement, dissolution behavior, pharmaceutical applicability, and future development potential.

MATERIALS AND METHODS

Formulation design and mechanism of solubility enhancement

The TPGS micellar system and PEG4000 solid dispersion system were prepared to improve AZP solubility through fundamentally different mechanisms.

TPGS is an amphiphilic molecule consisting of a lipophilic Vitamin E moiety and a hydrophilic PEG chain; upon reaching the CMC, TPGS molecules self-assemble into nanosized core-shell structures. AZP is incorporated into the hydrophobic core, thereby increasing its apparent aqueous solubility while maintaining colloidal stability. The drug remains molecularly dispersed within the micellar core and is protected from direct exposure to the aqueous environment.

In contrast, PEG4000 solid dispersions rely primarily on improved wettability and reduction in drug crystallinity. During solvent evaporation, AZP becomes dispersed within the hydrophilic polymer matrix. Upon contact with the dissolution medium, PEG4000 rapidly hydrates, improving drug wetting and facilitating dissolution. Furthermore, partial conversion of AZP from a crystalline to an amorphous state contributes significantly to enhanced drug release.

Preparation of PEGylated (PEG4000) solid dispersion

PEG4000 solid dispersions were prepared employing the solvent evaporation technique.

Predetermined quantities of AZP and PEG4000 were accurately weighed in various drug-to-polymer ratios, namely 1:1, 1:2, and 1:3.The accurately weighed components were dissolved in a common volatile organic solvent under continuous magnetic stirring to obtain a clear homogeneous solution. Subsequently, solvent evaporation was carried out under controlled conditions at ambient temperature until complete removal of solvent was achieved. The resulting solid mass was collected and dried under vacuum to remove residual solvent. The dried mass was pulverized gently using a mortar and pestle, passed through a suitable sieve to obtain uniform particle size distribution, and stored in a desiccator until further characterization.[1,2]

Preparation of TPGS micellar formulations

TPGS micelles containing AZP were prepared by dissolving the required amount of TPGS in deionized water and equilibrating the dispersion at 25°C for 24 h. The micelle size and polydispersity index (PDI) were subsequently determined using dynamic light scattering (DLS) (Nano ZS, Malvern Instruments, UK) on undiluted samples with a He-Ne laser at a scattering angle of 130°, and the data were analyzed using the CONTIN method. For potential drug loading, excess AZP was added to the fixed volume of micellar dispersion and equilibrated under orbital stirring at 37°C for 48 h. The dispersion was filtered through a 0.20 µm membrane filter to remove unentrapped drug, after which the concentration of AZP was quantified using ultraviolet-visible spectrophotometry (Shimadzu 3092, Japan). The physical stability of AZP was evaluated by incubating the formulation at 37°C under shaking conditions, followed by periodic filtration through a 0.22 µm membrane and analysis of drug precipitation over time. The localization of AZP within the micellar structure was investigated using pyrene fluorescence quenching studies, wherein pyrene (5×10^{-7} M) was incorporated into the micelles, and the dispersion was titrated with increasing concentrations of AZP. Changes in the fluorescence intensity ratio of the first and third vibronic peaks (I_1/I_3) of pyrene emission spectra were monitored to assess the microenvironmental polarity and determine the localization of AZP within the micelles.[2]

Evaluation and comparative analysis

A comparative evaluation of PEG4000-based solid dispersions and TPGS micellar formulations was performed to investigate the potential effect of our approach of enhancing the solubility using different solubility enhancement strategies for AZP for better therapeutics.[4,22] The comparison was carried out using formulation-related, physicochemical, and performance-based parameters reported for both delivery systems. Particular emphasis was placed on understanding the influence of formulation architecture on drug incorporation, solubilization behavior, and dissolution performance.[14,19]

Comparative assessment of formulation characteristics

The two formulation systems were compared with respect to carrier composition, formulation architecture, and preparation methodology. PEG4000 solid dispersions were evaluated as polymer-based solid-state systems prepared by solvent evaporation, whereas TPGS formulations were assessed as self-assembled nanosized micellar systems formed in aqueous media. The influence of these formulation approaches on the incorporation and stabilization of AZP was comparatively analyzed.[1,2]

Comparative assessment of drug incorporation and stabilization

Drug incorporation characteristics were evaluated based on the mechanism through which AZP was accommodated within the carrier systems. For PEG4000 solid dispersions, drug incorporation was assessed through molecular dispersion of the drug within the hydrophilic polymer matrix by evaluating the drug loading capacity of both approaches. For TPGS micelles, incorporation was evaluated through solubilization of AZP within the hydrophobic micellar core. Drug loading behavior, entrapment efficiency, and

drug localization characteristics reported for the respective systems were comparatively analyzed.

Comparative physicochemical characterization

Physicochemical characterization of the formulation was compared using respective analytical techniques. Previously, the PEG4000 solid dispersion system was evaluated using Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRD) to investigate drug-polymer compatibility, functional integrity, and solid-state transformations. The TPGS micellar system was evaluated for particulate dispersity using DLS and fluorescence spectroscopy to determine particle size distribution, PDI, and drug localization within the micellar structure. The obtained characterization data were comparatively interpreted to assess the influence of both formulations on drug stabilization.

Comparative evaluation of drug release and dissolution performance

The release behavior of AZP from both formulation systems was compared using the reported *in vitro* dissolution and release studies. Dissolution enhancement achieved through amorphization and improved wettability in PEG4000 solid dispersions was compared with the controlled release characteristics provided by TPGS micellar encapsulation. Comparative assessment was performed based on the extent of drug release and overall release profile observed for each formulation.

Comparative analysis of solubility enhancement mechanisms

The mechanisms responsible for enhancing the apparent solubility of AZP were comparatively evaluated. In PEG4000 solid dispersions, enhancement was attributed to improved wettability, reduced crystallinity, and increased surface area of the drug. In TPGS micelles, enhancement was attributed to micellar solubilization, particle size, and partitioning of AZP into the hydrophobic core of the self-assembled nanostructures. The contribution of these mechanisms toward improving drug dissolution and delivery performance was critically analyzed.

RESULTS AND DISCUSSION

Comparative analysis of formulation design and solubility enhancement strategy

Both formulation approaches were developed to overcome the poor aqueous solubility of AZP, a BCS Class II drug characterized by dissolution-limited oral absorption. However, the two systems employed fundamentally different solubilization mechanisms. The PEG4000 formulation utilized a solid dispersion approach in which the drug was molecularly dispersed within a hydrophilic polymeric carrier, whereas the TPGS system relied on spontaneous self-assembly of amphiphilic D-α-tocopheryl PEG into nanosized micelles capable of encapsulating the drug molecules within a hydrophobic core.[11,12]

The solid dispersion strategy primarily enhanced dissolution through improved wettability, reduction of crystallinity, increased surface area, and partial amorphization of the drug within the PEG4000 matrix. In contrast, TPGS micelles enhanced apparent solubility through micellar solubilization that exhibited a CMC of approximately 0.002% w/v, as determined by pyrene fluorescence spectroscopy and surface tension measurements, where the hydrophobic Vitamin E core served as a reservoir for AZP while the PEG shell stabilized the system in aqueous media.[8,9] The low CMC indicates a strong tendency for self-assembly and suggests that micellar integrity can be maintained even under extensive dilution conditions. Furthermore, TPGS demonstrated a high cloud point of approximately 74°C, indicating excellent thermal stability and suitability for pharmaceutical applications.

Unlike the micellar system, PEG4000 solid dispersions did not require micelle formation or self-assembly. Instead, enhancement of AZP performance was achieved through physical dispersion of the drug within the polymeric carrier matrix, thereby improving wettability and reducing crystallinity. The distinct formulation architecture of the two systems ultimately dictated their drug incorporation behavior and release characteristics.

Comparative drug incorporation and solubilization

The mechanism of drug incorporation differed substantially between the two formulation approaches. In the TPGS system, AZP was incorporated within the hydrophobic core of the self-assembled micelles. Fluorescence quenching studies using pyrene confirmed localization of AZP within the non-polar micellar core, demonstrating effective partitioning of the drug into the hydrophobic domain of the carrier. Such localization provides protection from the aqueous environment and contributes to improved drug stability and sustained release behavior.

Quantitative evaluation of the micellar system demonstrated an entrapment efficiency of approximately 86%, indicating highly efficient encapsulation of AZP within the micelles. Drug loading was approximately 9%, reflecting the finite volume available within the hydrophobic core for drug accommodation, as shown in Figure 1a.

Unlike the micellar solubilization-based encapsulation approach, solid dispersion potentially involved drug dispersion. Drug incorporation occurred through molecular dispersion of AZP within the hydrophilic polymer matrix during solvent evaporation. The enhanced % drug content

[Figure 1b] observed in the PEG4000 formulations was therefore attributed to improved drug distribution, increased wettability, and reduction in crystallinity rather than encapsulation efficiency. Consequently, while the TPGS system functioned as a true nanocarrier with defined drug-loading characteristics, the PEG4000 system acted as a solid-state solubility enhancement platform.

Comparison of physico-chemical characteristics

Physicochemical characterization revealed substantial differences between the two formulation systems.

DLS analysis demonstrated that blank TPGS micelles possessed a hydrodynamic diameter of approximately 11 nm, while after incorporating AZP, the particle size increased to approximately 20 nm, which potentially indicates an enhanced hydrodynamic diameter after drug loading. Overall, the micelles exhibited particle sizes ranging between 9.99 and 13.51 nm with PDI values below 0.3, indicating a narrow and monodisperse size distribution. Transmission electron microscopy micrographs further confirmed the formation of spherical and uniformly dispersed nanostructures without evidence of aggregation. These findings indicate successful self-assembly of TPGS into stable nanosized carriers suitable for drug delivery applications [Figure 2].

In contrast, the PEG4000 system was characterized using FTIR, DSC, and XRD analyses, as shown in Figures 3-5. FTIR studies demonstrated preservation of the characteristic functional groups of AZP without the appearance of additional peaks, indicating the absence of significant chemical interaction between AZP and PEG4000 [Figure 3]. DSC thermograms showed reduction or disappearance of the characteristic melting endotherm of AZP, suggesting a decrease in crystallinity following formulation [Figure 4]. XRD studies further confirmed reduction in diffraction peak intensity, indicating partial transformation of the drug into an amorphous form within the polymer matrix [Figure 5]. These physicochemical modifications are well-recognized contributors to enhanced dissolution behavior in solid dispersion systems.

Therefore, while TPGS micelles achieved solubility enhancement through nanostructural organization and drug encapsulation, PEG4000 solid dispersions relied on modification of the physical state of the drug.

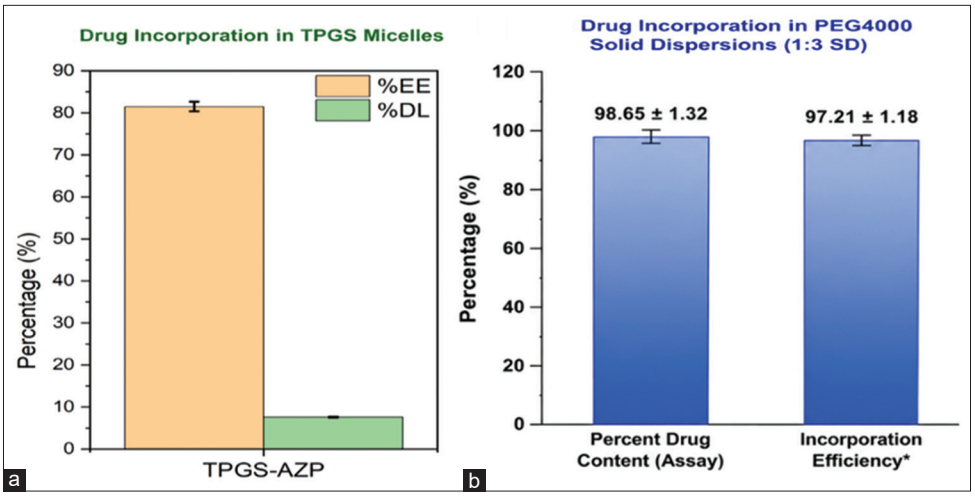


Figure 1: Drug incorporation of azelnidipine: (a) entrapment efficiency (%EE) and drug loading (%DL) in TPGS micelles; (b) drug content and incorporation efficiency of the PEG4000 solid dispersion (1:3 SD).

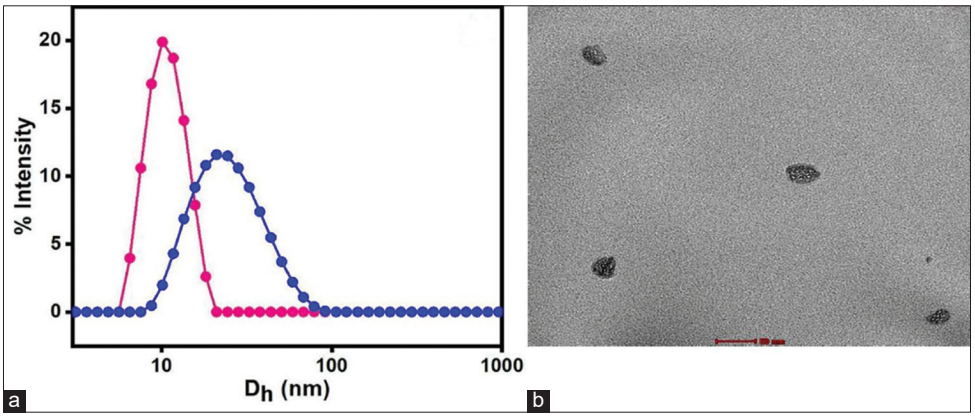


Figure 2: (a) DLS size distribution of blank and AZP-loaded TPGS micelles; (b) TEM image of TPGS micelles.

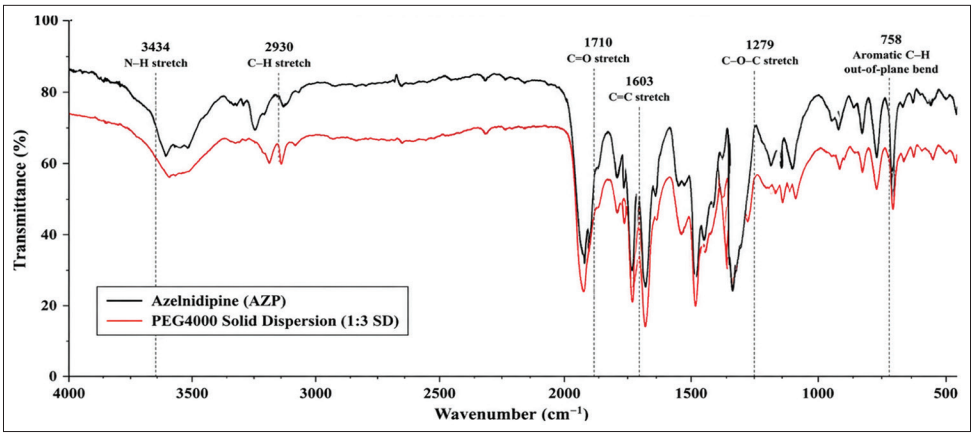


Figure 3: FTIR spectra of azelnidipine (AZP) and PEG4000 solid dispersion (1:3 SD).

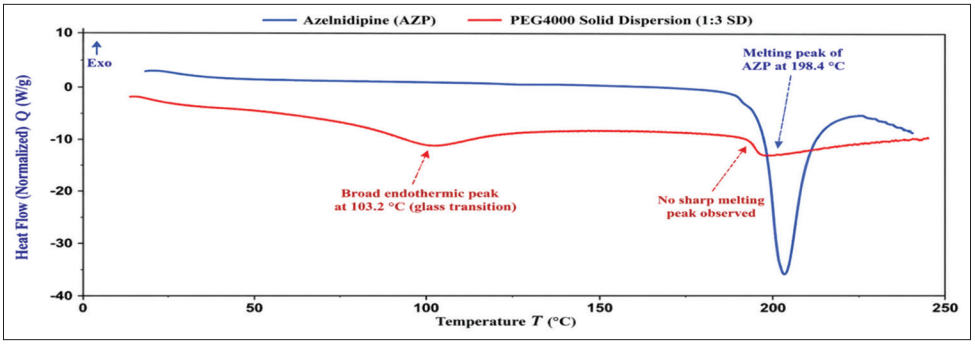


Figure 4: DSC thermograms of azelnidipine (AZP) and PEG4000 solid dispersion (1:3 SD).

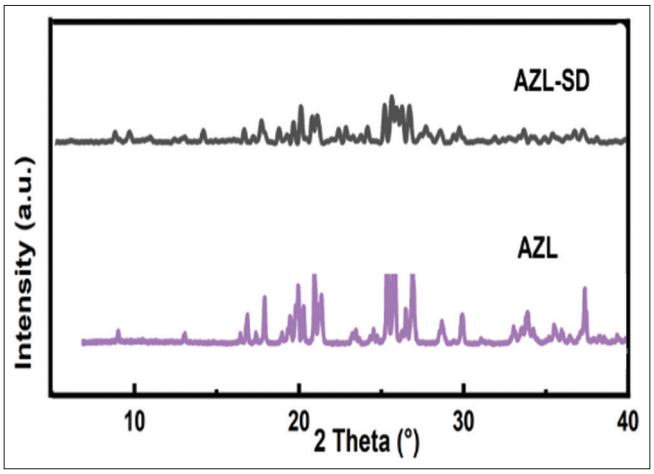


Figure 5: XRD patterns of pure azelnidipine (AZL) and PEG4000 solid dispersion (AZL-SD).

Comparison of drug release and dissolution performance

The most pronounced difference between the two systems was observed in their release behavior.

PEG4000 solid dispersions demonstrated rapid dissolution characteristics. Drug release values among the prepared formulations ranged from 60.27 ± 0.89% to 99.79 ± 2.36% within 30 min. The optimized formulation (S9) exhibited 99.79 ± 2.36% cumulative drug release at 30 min, indicating nearly complete dissolution of AZP. The substantial improvement in dissolution was attributed to increased wettability of the drug particles post-solid dispersion technique, an enhanced surface area, and reduction in crystallinity resulting from solid dispersion formation [Figure 6].

Conversely, TPGS micelles displayed a sustained-release profile. <20% cumulative drug release was observed over a period of 6 h, whereas free AZP exhibited approximately 90% release during the same period. The reduced release rate was attributed to localization of AZP within the hydrophobic micellar core, which acted as a diffusional barrier and restricted rapid drug diffusion into the surrounding medium.

These observations clearly demonstrate that PEG4000 solid dispersions are optimized for rapid dissolution and immediate drug availability, whereas TPGS micelles are better suited for controlled and sustained drug delivery applications.

Comparative advantages and limitations of PEG4000 solid dispersions and TPGS micelles

Both formulation strategies successfully addressed the poor aqueous solubility of AZP; however, each system exhibited distinct advantages.

The PEG4000 solid dispersion system provided almost complete dissolution (99.79% release within 30 min) through

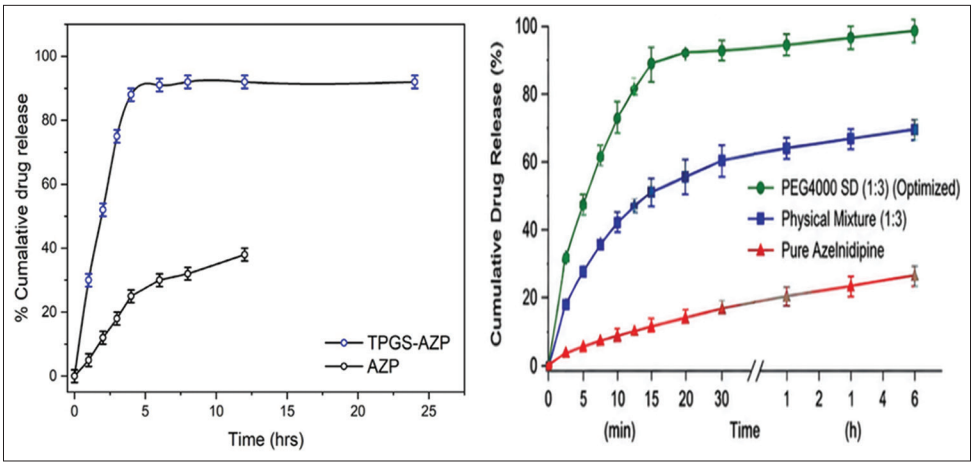


Figure 6: In vitro release profiles of AZP: TPGS micelles versus free drug (left); PEG4000 solid dispersion (1:3, optimized), physical mixture and pure drug (right).

a relatively simple manufacturing process involving solvent evaporation. The formulation approach is straightforward, scalable, and suitable for conventional oral dosage forms. However, the system does not provide controlled release and may be susceptible to recrystallization during long-term storage.

In contrast, TPGS micelles exhibited excellent nanocarrier characteristics, including a low CMC (0.002% w/v), nanosized particle dimensions (9.99–13.51 nm), high entrapment efficiency (86%), and stability upon dilution. The micellar system also provided sustained drug release with <20% release over 6 h, making it attractive for prolonged drug delivery applications.[1,2] Nevertheless, the relatively low drug loading (~9%) and greater formulation complexity may limit large-scale manufacturing compared with solid dispersion systems.

Overall, the comparative analysis indicates that PEG4000 solid dispersions are more suitable for immediate-release oral delivery of AZP, whereas TPGS micelles offer significant advantages for sustained release and nanocarrier-mediated solubilization. The choice of formulation strategy should therefore be guided by the intended therapeutic objective and desired release profile.

CONCLUSION

The present comparative study demonstrated that both PEG4000-based solid dispersions and TPGS micellar systems effectively improved the pharmaceutical performance of AZP through distinct formulation mechanisms based on enhancement of physic-chemical properties of the drug. PEG4000 solid dispersions enhanced drug dissolution primarily through improved wettability, increased surface area, and reduction in drug crystallinity, resulting in rapid drug release with the optimized formulation, which achieved rapid dissolution within 30 min. In contrast, TPGS micelles provided efficient nanoscale drug encapsulation with a low CMC (0.002% w/v), particle size ranging from 9.99 to 13.51 nm, and high entrapment efficiency (86%), thereby enabling sustained drug release with <20% cumulative release over 6 h.

The comparative findings indicate that PEG4000 solid dispersions are more suitable for immediate-release oral delivery systems where rapid dissolution and enhanced bioavailability are desired. Conversely, TPGS micelles offer significant advantages for controlled drug delivery owing to their nanoscale dimensions, excellent colloidal stability, high drug encapsulation efficiency, and sustained release characteristics. Therefore, the selection of an appropriate formulation strategy should be guided by the intended therapeutic objective, desired release profile, and dosage form requirements.

Overall, both approaches represent promising and complementary solubility enhancement technologies for poorly water-soluble drugs such as AZP. The present comparative evaluation provides valuable insight into the strengths and limitations of each system and may assist formulation scientists in selecting suitable carrier platforms for future development of hydrophobic therapeutic agents.

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Source of Support: Nil. **Conflicts of Interest:** None declared.