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Original Article

Fabrication and Comparative Assessment of Solid Dispersion and Nanosuspension in Solubility Enhancement of Antihypertensive Drug

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ABSTRACT

Background: Azilsartan, a poorly soluble angiotensin receptor blocker belonging to BCS class II, faces challenges related to low solubility and bioavailability. To address these issues, this study compares two formulation approachessolid dispersion and nanosuspension-aimed at enhancing the solubility and bioavailability of Azilsartan. **Materials and Methods:** Nine batches of Azilsartan-solid dispersion were prepared using spray drying with HPMC E5 LV, while nine batches of nanosuspension were formulated via solvent evaporation with PVPK-30. The formulations were evaluated for particle size, polydispersity index, zeta potential, X-ray diffraction pattern, morphology, solubility, and *in vitro* drug release. The optimal batches, solid dispersion-6 and nanosuspension-6, were selected based on drug content and entrapment efficiency for further comparative evaluation. **Results:** Solid dispersion-6 and nanosuspension-6 exhibited drug content of 93.23% and 95.71%, respectively. The particle sizes measured for solid dispersion-6 and nanosuspension-6 were 511.4 nm and 347.6 nm, respectively. Morphological differences between the formulations were evident in photomicrographs. Drug dissolution rates were 95.25% for solid dispersion-6, 96.14% for nanosuspension-6, and 98.14% in an *in vitro* dissolution study. **Conclusion:** The nanosuspension showed greater improvement in solubility and bioavailability, highlighting its potential as a nanocarrier for Azilsartan in clinical applications.

Keywords: Azilsartan, Solid dispersion, Nanosuspension, Solubility, Hypertension.

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INTRODUCTION

One of the biggest challenges for developing novel chemical entities and generics is their poor water solubility. Most potential new medication candidates have this undesirable physicochemical trait. Oral absorption and bioavailability are constrained because of the slow solubility of these substances.[1] Common methods used to enhance drugs' biopharmaceutical properties include micronization, nanosizing, crystal engineering, the application of solid dispersions, molecular or lipid encapsulations, and the formulation of microemulsions and self-emulsifying drug delivery systems. Water solubility and *in vivo* bioavailability are taken into account in the biopharmaceutics categorization system.[2] Taking into account solubility and intestinal permeability, BCS estimates the oral medicine absorption of solid dose forms. AZL is a Class II BCS material due to its low water solubility and high permeability. Classified as an Angiotensin Receptor Blocker (ARB), it targets the AT1 subtype of the angiotensin II receptor. The new antihypertensive medication AZL received initial FDA approval in February 2011. AZL's absolute bioavailability is anticipated to be 60%. Considering solubility and intestinal permeability, BCS estimates the oral medicine absorption of solid dose forms. AZL is a Class II BCS material due to its low water solubility and high permeability. Classified as an Angiotensin Receptor Blocker (ARB), it targets the AT1 subtype of the angiotensin II receptor. The new antihypertensive medication AZL received initial FDA approval in February 2011.[3,4] T_{max} might be anything from 1.5 hr to 3 hr. Two major inactive metabolites, M-I and M-II, are produced when AZL is metabolized. The most prevalent metabolite in plasma is M-II, which results from CYP2C9-mediated O-dealkylation. The decarboxylation catalysed by CYP2C8 and CYP2B6 results in the minor metabolite M-I. Multiple technologies have been used to hasten AZL's demise.[5] Since crystalline SDS has great stability and dissolving properties, it is being used more frequently as the number of chemical compounds with low solubility rises.[6] For solid dispersion intermediates, spray drying and hot melt extrusion have been the most popular methods of preparation in recent years.[7] The report claims that physical mixing of the drug

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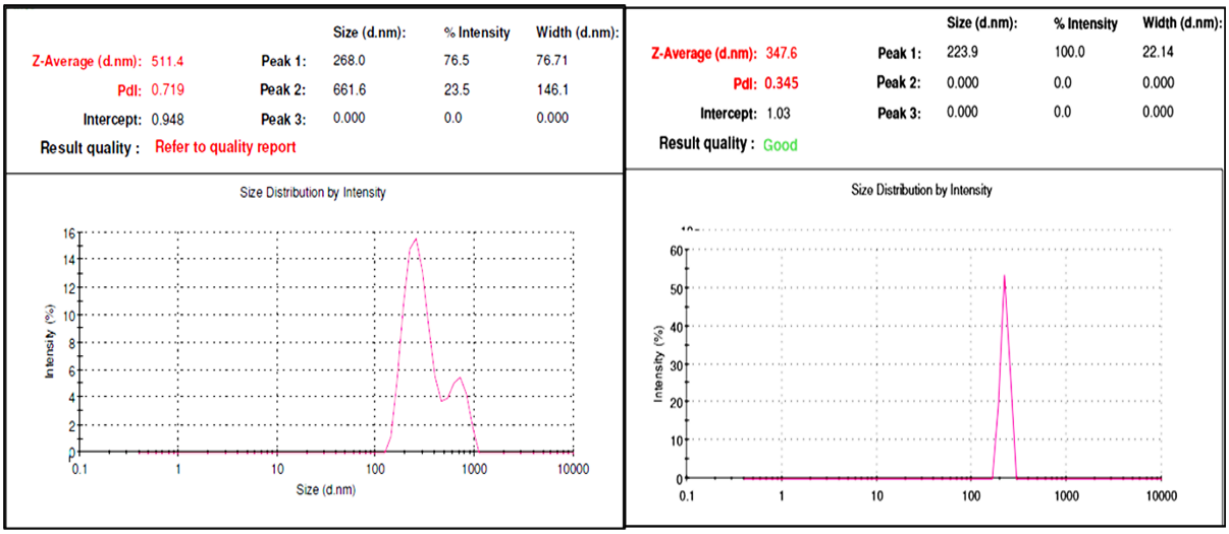
and the vehicle cannot produce stable dispersions.[8] Spray-drying is a better way to remove solvent water and make solid dispersion using polymer carriers and surfactants as drug supports. It has lower potential toxicity but a limited drug loading capacity.[9] Similarly, NSP is a game-changing nanotechnology approach to making poorly soluble medicines more palatable. Nanoparticle Stabilisation Particles (NSPs) are surfactant-stabilised colloidal submicron dispersions of nanoparticles.[10] Because there is no matrix material in the suspension, this medication is not water-soluble. This may be used to improve the solubility of drugs that aren't very soluble in water or oil.[11] Most NSPs are created using one of three processes: precipitation, high-pressure homogenization, or the solvent evaporation procedure with a stabiliser and co-stabilizer.[12] Because of its low water solubility, AZL may be helped by using either solubility-enhancing techniques (SDS or NSP). As a result, an effort was undertaken in this research to evaluate SDS and NSP formulations for their ability to improve solubility. In the current study, a design matrix was used to create SDS and NSP formulations. Nine iterations of each formulation were created by altering the concentration of HPMC E5 LV in SDS and PVP K 30 in NSP. After that, the drug loading, particle size, polydispersity index, zeta potential, X-ray diffraction pattern, formulation shape, solubility, and drug release *in vitro* were all checked for both formulations. The assessments led to the selection of the optimal formulation for



A) PS and PDI of SDS. **B) PS and PDI of NSP.**

Figure 1: PS and PDI of SDS and NSP.

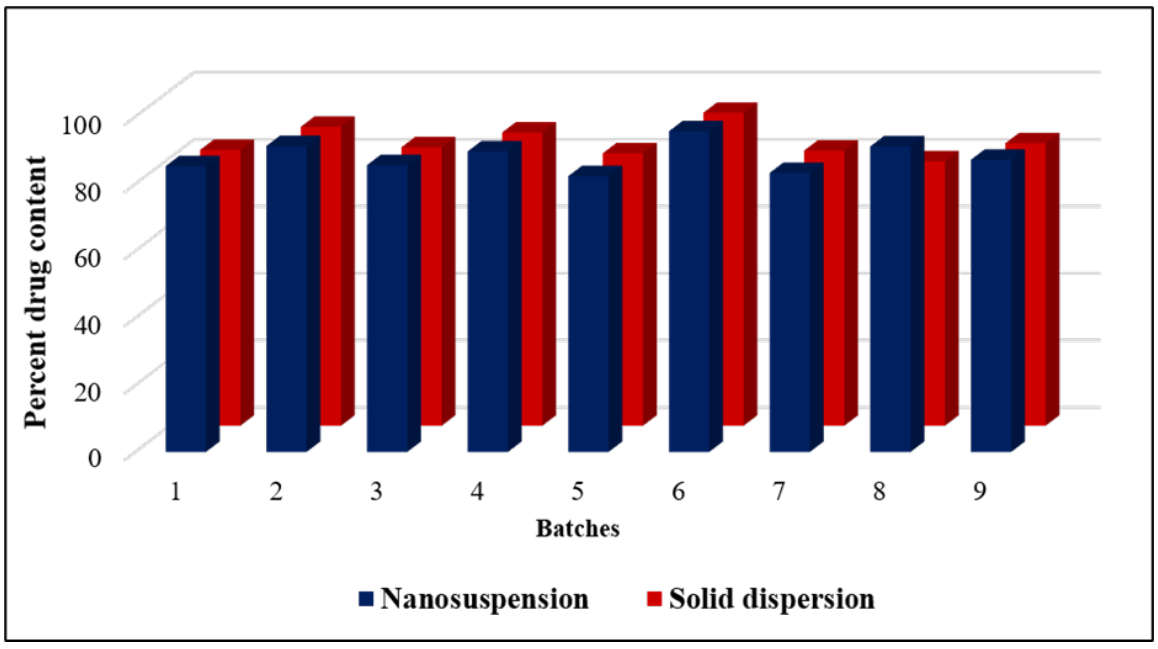


Figure 2: Percent drug content of SDS and NPS.

Table 1: Design matrix of AZL-SDS formulation.

Batches Code	Components			
	AZL (mg)	HPMC E5 LV (mg)	Ethanol (mL)	Purified water (mL)
SDS1	40	30	50	50
SDS 2	40	40	50	50
SDS 3	40	50	50	50
SDS 4	40	30	50	50
SDS 5	40	30	50	50
SDS 6	40	50	50	50
SDS 7	40	40	50	50
SDS 8	40	30	50	50
SDS 9	40	50	50	50

Table 2: Design matrix of AZL-NSP formulation.

Batches Code	Components					
	AZL (mg)	PVP K30 (mg)	Tween 80 (mL)	Methoanol (mL)	Purified water (mL)	String speed (rpm)
NS1	40	20	2.0	30	70	3500
NS2	40	30	3.0	30	70	3500
NS3	40	40	4.0	30	70	3500
NS4	40	20	4.0	30	70	3500
NS5	40	40	3.0	30	70	3500
NS6	40	30	4.0	30	70	3500
NS7	40	40	3.0	30	70	3500
NS8	40	20	2.0	30	70	3500
NS9	40	30	4.0	30	70	3500

solubility improvement. In what follows, we'll go further into the study's methodology as well as its findings.

MATERIALS AND METHODS

Materials

The azelsartan was purchased from Acura Labs Pvt. Ltd., Hyderabad, India. Sigma Aldrich (India) supplied us with some PVP K 30 and HPMC E5 LV. The company in Mumbai, India known as Loba Chemi Pvt. Ltd., supplied the Tween 80. From Merck Pvt. Ltd., in Mumbai, India, we ordered some ethanol.

Methods

The SDS and NSP were prepared by spray drying and solvent evaporation as discussed in the subsequent section.

Preparations of SDS

Based on the solubility and drug excipient investigation, HPMC E5 LV polymer was chosen for the spray drying preparation of nine batches of AZL-SDS. Table 1 shows the results of dissolving AZL (40 mg) and HPMC E5 LV (in different concentrations) in ethanol (50 mL) and water (50 mL), respectively. The mixture was stirred for 20 min before being sprayed with (Büchi B-290, Büchi Labortechnik AG, Switzerland). It was determined that an intake temperature of 130°C, an exit temperature of 90°C, a feeding rate of 3 mL/min, an atomizing air pressure of 3000 psi, and a nitrogen gas flow rate of 600 L/hr with 100% aspiration would provide the best results from the spray dryer.[13]

Preparation of NSP

NSP was manufactured using the solvent evaporation technique with a stabilizer and co-stabilizer. In a nutshell, the organic phase consists of (30 mL) methanol in which (40 mg) AZL has been dissolved. This was mixed into a stabilizing solution of PVP K30 surfactant and Tween-80 (70 mL) in water. After combining the two solutions, the volatile solvent was allowed to evaporate by leaving the mixture at room temperature while being stirred at 501°C (3500 rpm) for 30 min. The resultant NSP was stored at 4-8°C until further analysis (Table 2).[14]

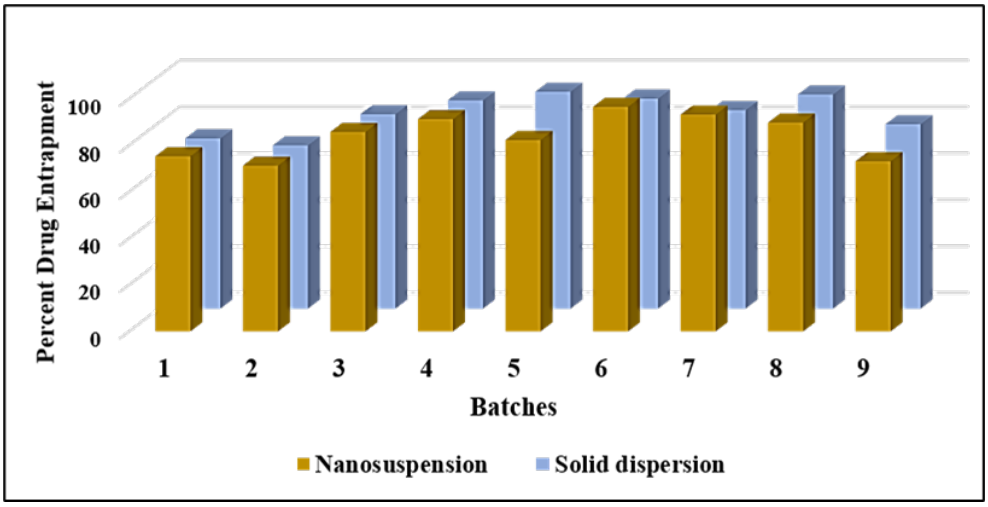


Figure 3: Percent drug entrapment of SDS and NSP.

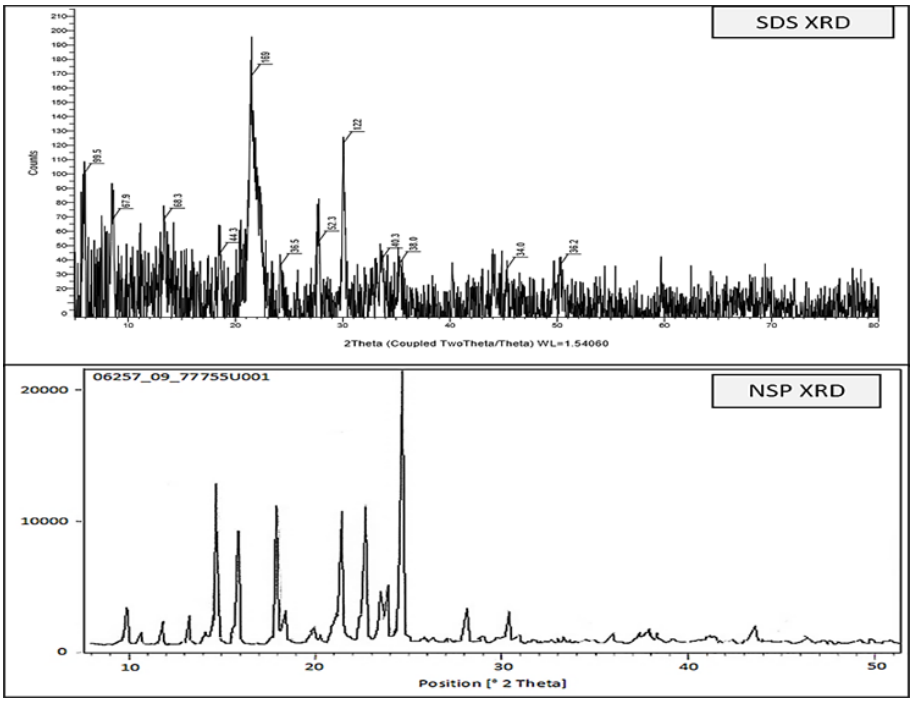


Figure 4: X-ray diffractogram of SDS and NSP.

Lyophilization of Selected NSP

Solid dosage forms, such as tablets, capsules, pellets, and effervescent tablets, need nanosuspension solidification for long-term stability. Lyophilization (freeze drying), one of the solidification methods, was used after the PS, PDI, and ZP of NSP were measured. D (-) (-) The manufactured formulation included mannitol as a cryoprotectant. The selected proportion of NSP to mannitol (in terms of weight) was one to one. About 2 g of NSP was lyophilized by first being frozen at 80°C for 2 hr, then being freeze-dried at 50°C under 0.021 mbar pressure for 48 hr (Virtis, Benchtop, Mumbai, India).[15]

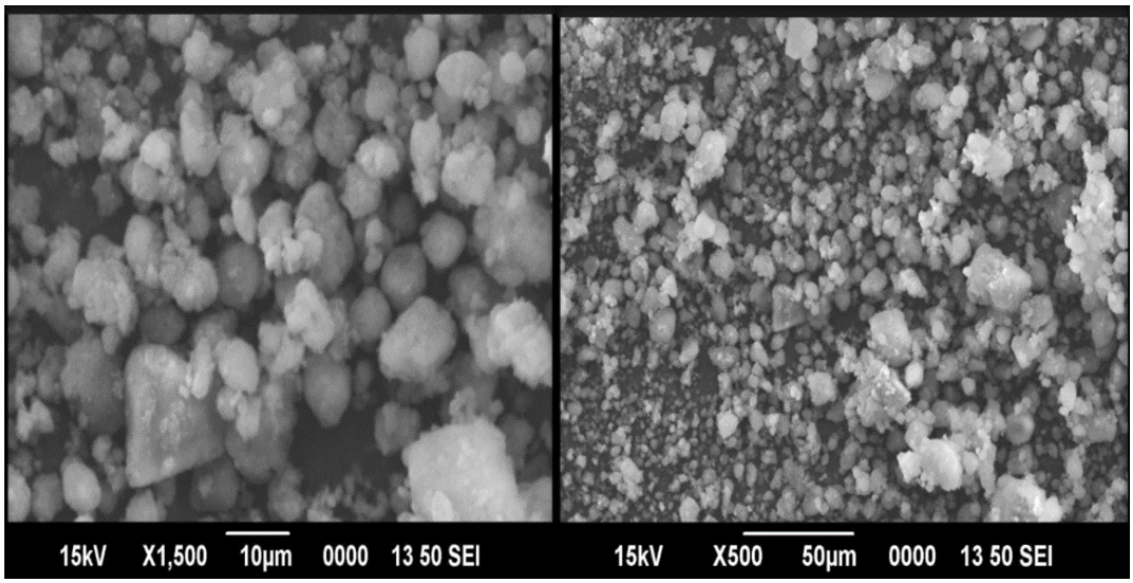
Evaluations of SDS and NSP Formulation

Percent Drug Content

Drug concentrations were determined by completely dissolving 1 mL of SDS and NSP formulations in methanol. Spectrophotometric analysis (UV 1700, Shimadzu, Japan) at 246 nm was used to determine the amount of AZL present in the methanolic extract. Concentration vs drug content in percentage form was displayed on the calibration graph.[16]

Percent Entrapment Efficiency (%EE)

The quantity of medication that was successfully encapsulated inside the formed spheres was determined by the percent EE. The AZL concentrations in the SDS and NSP were also measured



A) SEM images of SDS-6. **B) SEM image of NSP-6.**

Figure 5: SEM photomicrograph of both formulations.

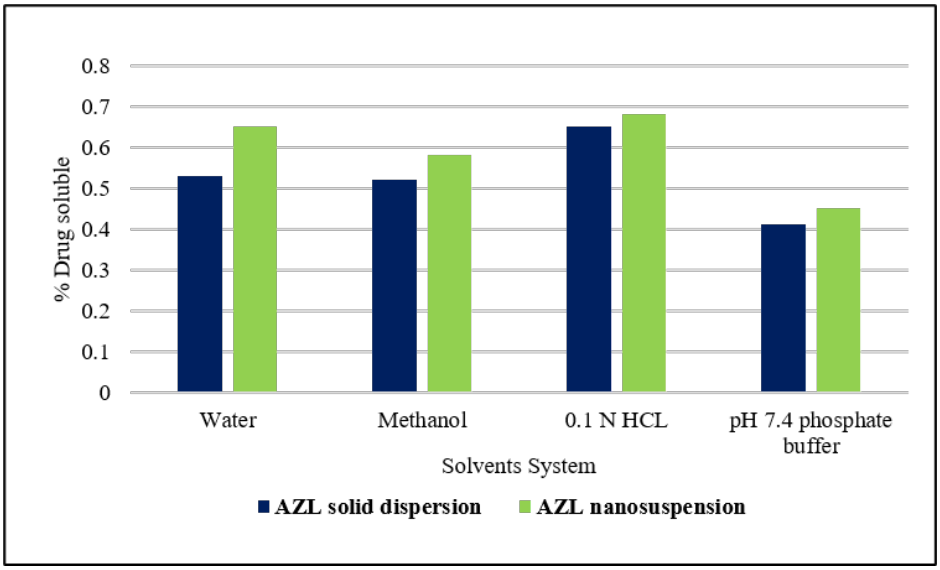


Figure 6: Solubility study of SDS-6 and NSP-6.

by ultracentrifugation at 12,000 rpm for 2 hr using a (Bachman Coulter USA). The clear supernatant was added, and then an aliquot was diluted 1:10 (v/v) before its spectrophotometric absorbance at 246 nm was measured (UV 1700, Shimadzu, Japan). The percentage EE was determined using the following equation (1).[17]

$$\%EE = -\frac{Amount\ of\ drug\ added - Amount\ of\ drug\ in\ supernatant}{Amount\ of\ drug\ added} \times 100 - - - - - -(1)$$

Determination of Particle Size, Polydispersity Index, and Zeta Potential

Because of its ability to enhance medication solubility and oral absorption, Particle Size (PS) is an important parameter for effective SDS and NSP formulation. Using a Nano ZS90 from (Malvern Instrument Ltd., UK) and a 5mW neon laser, we were able to determine the typical PS and Polydispersity Index (PDI) as showing in Figure 1. The experiment lasted 180 sec and was performed at 25°C in an inflatable polymeric cell that measured 10 mm in diameter. After diluting the samples by a factor of ten with distilled water, they were studied at room temperature.[18]

X-ray Diffraction (XRD) study

XRD analysis was performed on lyophilized SDS and NSP coarse powder to identify structural alterations caused by AZL loading. For XRD analysis, a 1-degree-per-minute scan rate was used

throughout a 2-degree-by-3-degree-by-90-degree range (Rigaku Ultima IV, Japan).[19]

Morphological Study

Scanning Electron Microscopy (SEM) was used to examine the lyophilized SDS and NSP for morphological changes. After overnight room temperature drying, both samples were scanned with an electron beam at 20 kV after being placed on double-sided tape on copper stubs and coated with platinum.[20]

Solubility Study

Both formulations and pure AZL were tested for their solubility in a phosphate buffer at a pH of 1.2. 10 mL of phosphate buffer were placed in teflon-facing, screw-capped vials, and AZL powder, a physical combination, and both formulations were added to evaluate their solubility. In an orbital shaking incubator (CIS-24, Remi instrument, Mumbai, India), the vials were kept at equilibrium for 24 hr at 370.5°C and 100 rpm. By employing a 0.22 m membrane filter (Merck Millipore®, Germany) and a UV spectrophotometer (1700, Shimadzu, Japan), we were able to filter the contents of the vials and quantify their absorbance at 246 nm.[21]

In vitro Dissolution Study

All three of these substances, AZL, its SDS, and its NSP, were tested for solubility *in vitro* using a dialysis bag and a himedia dialysis membrane (MWCO 12 KD). Dialysis bags were pre-treated and then optimized NSP formulations containing 40 mg of AZL were placed inside. The medication was dissolved in 900 cc of dissolve medium using USP dissolving equipment II operated at 37 0.5°C and 100 rpm paddle speed. Drug release assays in 0.1 N HCl (pH 1.2) environment compared the enhanced formulations of AZL NSP and SDS to pure drug. 5 mL samples were taken at regular intervals (between 5 and 120 min) and then discarded and refilled with new dissolving media. The materials were analyzed using a 246 nm UV spectrophotometer after being filtered.[22]

RESULTS

Percent drug content

In order to create the nine distinct batches of NSP and SDS, the excipient concentrations were varied. There was a wide variation in the drug content of NSP lots, from 82.31 to 95.71%, with the highest drug level of any lot being detected in NSP 6. Drug content ranged from 80.12 to 93.23% across all batches, as shown by SDS. As may be shown in Figure 2, the drug content of SDS 6 was 93.23%. Therefore, batches of NSP6 and SDS6 were chosen as optimized batches from the developed formulations and subjected to further comparative evaluations.

Percent Entrapment Efficiency

In order to create the nine distinct batches of NSP and SDS, the excipient concentrations were varied. NSP 6 had the highest drug entrapment percentage (96.61%) among all batches. The other batches ranged from 71.3% to 96.61%. Drug entrapment ranged from 70.2% to 93.3% in SDS studies. Figure 3 shows that SDS 6 had the highest percentage of drug entrapment across all batches tested. Because of this, batches of the created formulations NSP6 and SDS6 were chosen as optimal and put through further comparison tests.

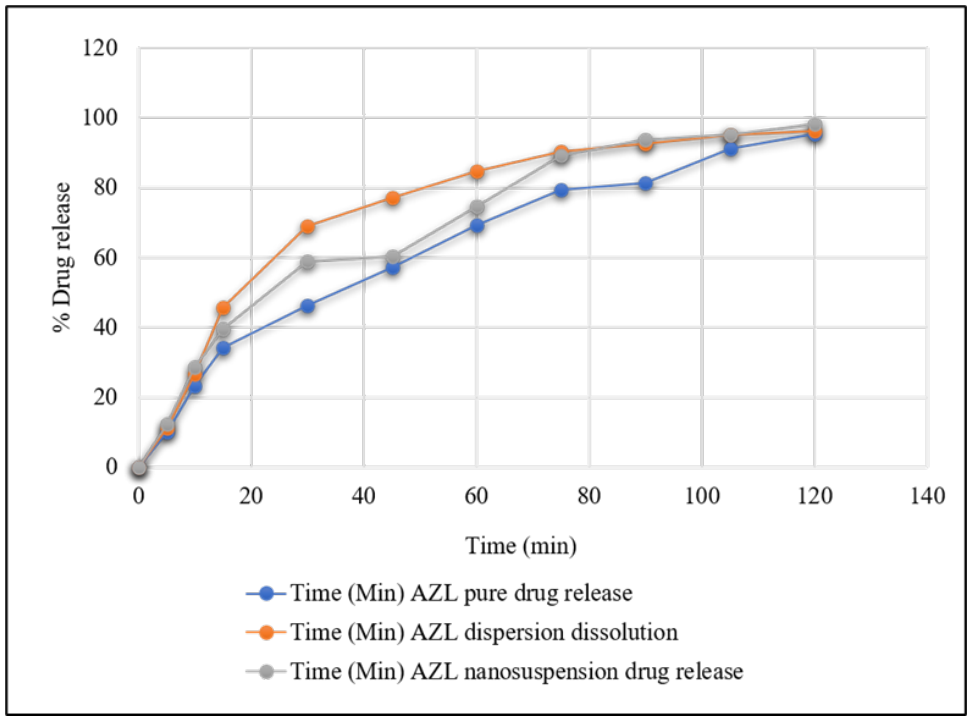


Figure 7: *In vitro* drug release profile of AZL pure drug, SDS-6 AND NSP-6.

Determination of Particle Size and Polydispersity Index

When it comes to dissolving medicinal molecules, the solubility of the formulation's PS is crucial. SDS-6 has a PS of 511.4 nm, whereas NSP-6's PS was 347.6 nm. Both formulations' PS variations were affected by the polymer concentrations, with HPMC E5 LV lowering PS more than NSP and PVPK30. Consequently, NSP was a more amenable formulation to AZL's improved solubility. The PDI was calculated by taking into account both the typical diameter of a PS and its distributional dispersion. SDS-6 and NSP-6 have PDI values of 0.719 and 0.34 Mw, respectively. In contrast to the high PDI value of SDS-6, which indicates a wide size distribution or various populations, the low PDI value of NSP-6 suggests high levels of homogeneity within the sample.

X-ray Diffraction Study

Crystalline structures were clearly visible in the X-ray diffractogram NSP-6, with notable peaks at 25.5 and 18.5, 17.9, 18.3, 19.1, 21.5, and 23.2. NSP-6's diffraction pattern mirrored that of AZL and PVP K 30, but with less pronounced peaks as a result of the particles' shrunken dimensions. Similarly, SDS-6 had a typical crystalline pattern with a prominent peak at 36.2, 99.5, 67.9, 68.3, 122, 52.340.3, and 169. As may be seen in Figure 4, the largest peak was at a (2) value of 169. The diffractogram of AZL dispersion, however, displays all of the key typical crystalline peaks. This suggests that the medication underwent a little amorphization.

Morphological Study

The morphological characteristics of the optimized solid dispersion (SD-6) and nanosuspension (NS-6) formulations were evaluated using Scanning Electron Microscopy (SEM). The SEM images revealed distinct differences in the surface morphology of the two formulations. Solid dispersion (SD-6) exhibited a relatively smooth and homogeneous surface, with irregularly shaped particles indicating partial amorphization of the drug. In contrast, the nanosuspension (NS-6) showed smaller, uniformly spherical particles with a rougher surface, which is consistent with the nanonization process. The reduced particle size and more uniform distribution in the nanosuspension formulation contributed to the improved solubility and dissolution rate. The SEM analysis confirmed that the nanosuspension provided a more refined particle structure compared to the solid dispersion, which may be responsible for the enhanced bioavailability of Azilsartan in the nanosuspension formulation as shown in Figure 5. These morphological observations aligned with the particle size measurements and dissolution studies, further supporting the superior performance of the nanosuspension.

Solubility Study

Both formulations were put through a solubility test to determine how well they dissolved in common solvents like water, methanol, 0.1N HCl, and phosphate buffer (pH 7.4). Figure 6 shows that the most advanced NSP-6 formulation benefited from the addition of PVPK-30, which also marginally increased the solubility of SDS-6 in all solvents. The data showed that the NSP formulation increased AZL solubility more than the SDS formulation.

In vitro Dissolution Study

Pure AZL demonstrated 95.25% drug release in an *in vitro* dissolution assay, whereas AZL SDS and NSP showed 96.14 and 98.14% drug dissolution, respectively as shown in Figure 7. Maximum drug release was seen in NSP as compared to pure drug and SDS, suggesting that the addition of PVP K 34 and Tween-80 to NSP improved the solubility of AZL. The NSP formulation improves AZL solubility, therefore, it may be utilized as a foundation for future oral AZL formulation research and development.

DISCUSSION

The low water solubility of many new chemical entities and generics is a major hurdle in their development. This unfavourable physicochemical feature is present in the vast majority of possible new drug options. The poor solubility of these compounds limits their oral absorption and bioavailability. To make medicines better at what they do, scientists often use micronization, nanosizing, crystal engineering, solid dispersions, molecular or lipid encapsulations, the creation of microemulsions, and the creation of self-emulsifying drug delivery systems. The biopharmaceutics classification scheme considers solubility in water and bioavailability in living organisms. Spray drying and solvent evaporation were used to create the SDS and NSP in this research. Excipient concentrations were manipulated to produce nine unique batches of NSP and SDS. The drug content of NSP lots ranged from 82.31% to 95.71%, with NSP 6 having the highest drug level of any lot. According to the SDS, the average drug concentration across all batches was 93.23%. The PS's solubility is critical when it comes to the dissolution of pharmaceutical compounds. The PS of SDS-6 is 511.4 nm, whereas the PS of NSP-6 was 347.6 nm. Polymer concentrations influenced PS variations in both formulations, with HPMC E5 LV reducing PS more than NSP and PVPK30. However, all the major characteristic crystalline peaks can be seen in the AZL dispersion diffractogram. This points to some amorphization of the drug having taken place. Water, methanol, 0.1 N HCl, and phosphate buffer (pH 7.4) were used in a solubility test to see how well each formulation dissolved in these common solvents. Figure 6 demonstrates that the incorporation of PVPK-30 into the state-of-the-art NSP-6 formulation improved the solubility of SDS-6 across the board by a small margin. The NSP formulation

improved the solubility of AZL more than the SDS formulation, according to the results. Due to its increased solubility of AZL, the NSP formulation may serve as a starting point for further studies and the development of oral AZL formulations.

CONCLUSION

The purpose of this research was to create an effective formulation to improve AZL's solubility. Both SDS and NSP were developed to their maximum potential. NSP had the lowest PS, PDI, and spherical shape of the particles. It also had the greatest *in vitro* drug dissolving rate and the largest solubility enhancement. The research shown that NSP of AZL might be a quick, cheap, and superior method to enhance solubility and bioavailability in an *in vivo* model. Research on using a similar strategy with other poorly soluble medicines may continue.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AZL: Azilsartan; **BCS:** Biopharmaceutics Classification System; **HPMC:** Hydroxypropyl Methylcellulose; **PVP:** Polyvinylpyrrolidone; **SDS:** Solid Dispersion System; **NSP:** Nanosuspension; **PS:** Particle Size; **PDI:** Polydispersity Index; **ZP:** Zeta Potential; **XRD:** X-ray Diffraction; **SEM:** Scanning Electron Microscopy; **UV:** Ultraviolet; **HCl:** Hydrochloric Acid.

SUMMARY

This study aimed to improve the solubility and bioavailability of Azilsartan, a poorly soluble angiotensin receptor blocker classified as BCS class II. Two formulation approaches, solid dispersion using HPMC E5 LV and nanosuspension using PVPK-30, were developed and compared. Nine batches of each formulation were prepared and evaluated for drug content, particle size, polydispersity index, zeta potential, and *in vitro* drug release. Solid dispersion-6 and nanosuspension-6 were identified as optimal, showing high drug content and entrapment efficiency. Nanosuspension-6 demonstrated superior solubility and drug release, suggesting its potential as an effective nanocarrier for improving Azilsartan's clinical efficacy.

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