Original Article

A 3^2 Factorial Design Approach for Formulation and Optimization of Azilsartan Medoxomil Nanosuspension for Solubility Enhancement

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ABSTRACT

Background: Azilsartan medoxomil (AZL) is an orally active nonpeptide angiotensin II receptor antagonist with less water solubility and oral bioavailability. **Objectives:** Increase the solubility and dissolving rate of AZL. **Materials and Methods:** For formulation we used a probe sonication approach to create nanocrystals. The impacts of independent factors such as % polymer concentration (X_1) and sonication duration (X_2 min) on dependent variables such as particle size (Y_1 nm) and % drug release (DR) were optimised using a 3^2 response surface methodology (Y_2). **Results:** The prepared batches were examined for size, polydispersity index (PDI), zeta potential, solubility study and dissolution study. AZL nanocrystal (PS2 batch) particle size and zeta potential was found to be 168 ± 10 nm, 0.314 ± 0.02 and - 22.72 ± 2.6 mV respectively. The batch (PS2) with the best results was chosen and subjected to additional testing. *In vitro* dissolution of all 13 batches and pure drug was in ranges of 51.98-81.99% and 11.23 %, respectively. **Conclusion:** The FTIR analysis indicated that AZL and soluplus have no physical interaction. DSC, XRD, and SEM investigations revealed that the crystalline form of the medication was converted to an amorphous form, resulting in an improve water solubility and dissolution rate. Thus the studies exhibited nanocrystals prepared by probe sonication method showed significant enhancement in solubility and dissolution rate.

Key words: Azilsartan medoxomil (AZL), Nanocrystal, Sonication, Solubility, Drug release.

INTRODUCTION

In whatever mode of administration, solubility is a critical element for medication therapy. Up to 40% of new medications developed by the researchers in recent years have been predicted to be poorly water soluble or lipophilic substances.[1] Unfortunately, due to solubility issues, many of these prospective medications are abandoned in the early phases of development. Poor solubility medications in gastrointestinal fluids are common causes of insufficient bioavailability. According to the BCS, increasing the drug's solubility and dissolution rate in gastrointestinal fluids can improve bioavailability, especially for class II (they are low solubility and high permeability) drugs. Because the drug release and solubility in the gastric fluid is rate limiting step for BCS class II drugs, rather than absorption, increasing solubility increases bioavailability.[2] As a result, it's critical to understand these medications' solubility issues and techniques for overcoming them so that the active compounds' potential therapeutic effects can be realised.[3] As a result, numerous efforts have been made to improve medication solubility.[4]

A number of approaches have been developed throughout the years to increase the solubility of medications that are poorly water soluble. Physical adjustments to the drug substance, chemical modifications to the drug substance, and other procedures are all examples of solubility improvement technique. These strategies can increase the aqueous solubility of poorly soluble medications. Nanosuspension is most favorable techniques for enhancing the solubility and dissolution rate of poorly water soluble drugs.[5]

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A nanosuspension is a colloidal dispersion of medication particles that is stabilised by surfactants and is submicron in size. A pharmaceutical nanosuspension is a liquid formulation containing very finely dispersed solid medication particles for oral, topical, parenteral, or pulmonary delivery.[6] Nanosuspension technology keeps the medicine in the appropriate crystalline state while reducing particle size, resulting in a faster dissolving rate and hence higher bioavailability.[7]

Azilsartan (AZL) is an angiotensin II receptor blocker (ARB) that is being useful in the treatment of hypertension. AZL is a typical BCS II medication, with low water solubility and a 60 % oral bioavailability. As a result, the current study were improved the bioavailability of a Azilsartan. AZL, by increasing its solubility, and it was found to be a viable model drug for nanosuspension creation. Nanosuspensions can be included into tablets, pellets, hydrogels, and suppositories, and are ideal for a variety of administration routes. Increased saturation solubility and, as a result, an increase in the drug's dissolving rate.[8] Increasing the amorphous proportion in the particles, which could result in a crystalline structural shift and increased solubility. The effects of independent variables such as polymer concentration (X_1%), sonication time (X_2 min), and dependent variables such as particle size (Y_1 nm) and DR were assessed using a surface approach 3^2 (three level-two factors) (Y_2%). For physicochemical assessment of nanosuspensions, researchers used Fourier transform infrared (FTIR), X-ray Diffraction, field scanning micrographs (FESEM), and *in vitro* drug release. In comparison to the pure form, the produced azilsartan- nanosuspensions have a greater solubility and dissolution rate.

MATERIALS AND METHODS

Materials

Azilsartan medoxomil was obtained as a gift sample from USV Pvt. Ltd., Mumbai, India. Soluplus was kindly supplied by BASF India Co., Ltd. (Mumbai, India). All other solvents and chemicals were of analytical grade and were obtained from Loba chemicals Pvt. Ltd, Mumbai, India and RCFL Limited, New Dehli, India.

Preparation of AZL Nanosuspension

Azilsartan medoxomil nanosuspensions were prepared according to probe sonication method. Nanosuspension of azilsartan medoxomil is prepared in thirteen different batches by varying the polymer ratio with stirring time, herein the concentration of drug kept constant. Firstly, azilsartan dissolved in organic solvent (such as methanol), Soluplus (polymer) dissolved in 50 mL distilled water. The Suspension gets homogenized by using mechanical stirrer at 1000 rpm for 15 min. The homogenized suspended solutions were sonicated at different time period as mentioned in Table 1 using probe sonicator. After complete verification of process parameters, total thirteen batches of AZL nanosuspension were prepared by probe sonication technique.[9]

Experimental design for optimisation

The statistical experimental investigation was conducted using the DESIGN-EXPERT software (Stat-Ease Inc., Minneapolis). The 3^2 (three level-two factor) response surface methodology was utilised for optimisation and detection of the impact of independent variables on responses. The polymer concentration (X_1) and sonication time (X_2 min) were chosen as independent

Table 1: Formulation composition for azilsartan medoxomil nanosuspension.

Batch Code	Polymer concentration (%)	Time (min)	Particle size (nm)	Drug release (%)
PS1	0.55	15	380	69.02
PS2	1	15	168	81.99
PS3	0.55	15	400	68.21
PS4	1	10	356	73.98
PS5	0.1	20	296	51.98
PS6	0.55	10	231	73.25
PS7	0.1	15	850	56.32
PS8	0.55	15	415	69.22
PS9	1	20	425	68.73
PS10	0.55	15	410	71.68
PS11	0.55	20	267	72.99
PS12	0.1	10	827	54.91
PS13	0.55	15	425	63.55

variables and changed at three levels: low (1) middle (0) and high (+1). Particle size (Y_1 nm) and % DR were chosen as dependent parameters (Y_2). The statistical design for selected dependent and independent variables is given in Table 1. For optimisation, the effect of independent variables (X_1;X_2) on dependent variables (Y_1;Y_2) was modelled by using the following equation:

$$Y = \beta_0 + \beta_1 x_1 + \beta_1 x_1 + \beta_3 x_1 x_2 + \beta_4 x_1^2 + \beta_5 x_2^2 \quad (1)$$

Where,

Y is the response, β_0 is the intercept and $\beta_1 - \beta_5$ is regression coefficients. $x_1 x_2$ are individual effects. $x_1 x_2$ is the interaction effect and x_1^2, x_2^2 are the quadratic effects. One-way ANOVA was used to evaluate the model's significance at the $P < 0.05$ level.[10]

CHARACTERISATION

Particle size and zeta potential

At room temperature, a Coulter LS 230 analyzer (Beckman Coulter Co., Ltd., USA) was used to perform laser diffraction. A Delsa 440SX zeta potential analyzer was used to assess the zeta potential of nanosuspension (Beckman Coulter Co., Ltd., USA).[11]

Solubility of AZL nanosuspension

In 20 ml of phosphate buffers pH 6.8 solutions containing conical flasks, 10 mg pure drug and 10 mg equivalent weight of produced nanosuspension were introduced separately and agitated at 37°C±0.5°C in mechanical orbital shaker (Remi mechanical shaking incubator, Bombay) for 24 hr. The mixes were filtered and examined in a UV spectrophotometer at 243 nm, which was the absorption maxima determined before, to estimate drug concentrations. All of the samples were analysed three times.[12]

Fourier transforms infrared spectroscopy

The FTIR analysis was used to look for any chemical interactions between the medication and the excipient. FTIR spectrometer was used to examine the FTIR spectra of pure azilsartan, soluplus, the physical mixture, and dried optimum nanosuspension (Shimadzu 8400S, Japan).

Differential scanning calorimetry (DSC)

DSC was evaluated the thermal behaviour of pure medication, soluplus, physical mixing, and optimized nanosuspension (DSC-60, Shimadzu and 821, Mettler Toledo).

X-ray powder diffraction (XRD)

The crystallanity of pure medication, soluplus, physical mixture, and optimized nanosuspension was determined using x-ray diffraction. Cu K radiation at a wavelength of 1.54 A was used for XRD in symmetrical reflection mode.

Scanning electron microscopy (SEM)

The particle surface morphology of nanosuspension was studied using SEM

In-vitro dissolution study

In USP type II dissolution equipment, drug release was performed. The test was performed at 50 rpm in 900 mL of phosphate buffer pH 6.8 as a dissolution media (at 37°C). In a 900 ml dissolving media, accurately weighed samples containing the equivalent of 10 mg azilsartan were disseminated. After that, samples of 5 mL were taken from the dissolution media at intervals of 5, 15, 30, 45, 60, 90, 120, and 150 min. To keep the sink state, the same volume of new medium was supplied to the dissolution vessel. A UV spectrophotometer with a wavelength of 243 nm was used to assess the amount of medication dissolved. Analysis of all the samples was done in triplicate.[13]

Stability study

The stability of the improved AZL nanosuspension was tested by placing the formulation in glass vials and storing them at ambient temperature (25±02C) and in the refrigerator (50±3C) for three months. After 3 months, zetasizer was used to visually inspect the samples for sedimentation and changes in particle size and size distribution.

RESULTS

Solubility studies of AZL nanosuspension

The solubility of the pure medication was 0.89 mg/ml, however it was substantially higher in nanosuspension. Table 2 demonstrates the solubility of various batches of nanosuspension. The maximum solubility of AZL medoxomil nanosuspension was found in PS2 i.e. 4.45 mg/ml. The solubility of nanosized AZL medoxomil was 4 time greater than that of pure AZL medoxomil. The result shows that the solubility of AZL medoxomil nanosuspension was much higher than that of the pure form.

Fourier transform infrared spectroscopy

The FTIR spectra of pure medication, soluplus, physical combination, and freeze dried optimised nanosuspension given in Figure 1. The pure polymer shows characteristic peaks at 2850 cm^{-1} is due to the

Table 2: The Solubility: Pure drug and prepared batches.	
Batch name	**Solubility (mg/ml)**
PS1	3.91±0.78
PS2	4.45±0.90
PS3	3.96±0.55
PS4	4.02±0.88
PS5	1.19±0.34
PS6	4.01±0.86
PS7	1.30±0.20
PS8	3.99±0.75
PS9	1.12±0.24
PS10	2.56±0.55
PS11	1.47±0.12
PS12	1.69±0.23
PS13	0.89±0.15

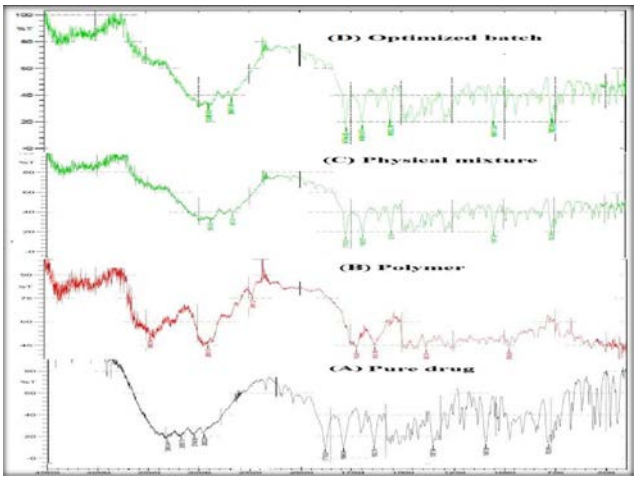


Figure 1: FTIR Spectrum of (A)Pure drug;(B)Pure Polymer; (C)Physical mixture.

C-H stretching vibrations and peak near to 1752 cm^{-1} is due to the C=O stretching. The two sharp peak at 1694 cm^{-1} and 1552 cm^{-1} is due to symmentric stretching of C=C and N-H group respectively. The pure polymer shows characteristic peaks at 2924 cm^{-1} of aliphatic-CH stretching. It also shows sharp peak at 1718 cm^{-1} and 1631 cm^{-1} (C=O stretching) and O-H peak at 3463 cm^{-1}. Physical mixture and optimized nanosuspension shows characteristic peaks of both at same wave number indicate of no interaction between drug and polymer.

Differential scanning calorimetry

DSC thermogram of AZL shows endothermic melting peak at 215.83°C see Figure 2. The pure polymer soluplus showed a broad glass transition (Tg) endotherm at 63°C. Physical mixture of drug and polymer exhibits

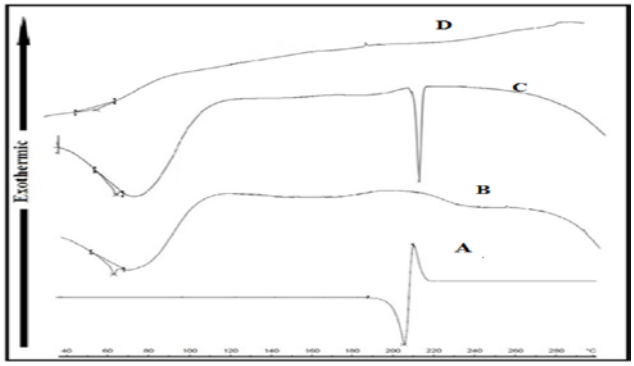


Figure 2: DSC thermograms of (A) AZL; (B) Soluplus; (C) Physical mixture; (D) Optimized batch.

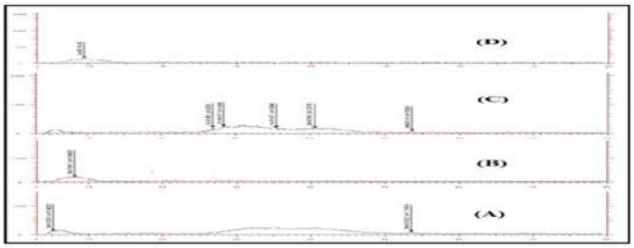


Figure 3: XRPD of (A)AZL; (B) Soluplus; (C) Physical mixture; (D) Optimized batch.

characteristic peaks of both drug and polymer. Freeze dried nanosuspension was shows peak of soluplus with much reduced intensity and absence of pure drug peak. The absence of drug peak in optimized nanosuspension indicates conversion of crystalline drug to amorphous form, which can be further confirmed by XRD.

X-ray powder diffraction

Figure 3 shows XRPD spectra of pure drug, soluplus, physical mixture and freeze dried nanosuspension. Optimized nanosuspension shows characteristic peak of soluplus while absence of halo peaks of pure drug. The absences of drug peaks in optimized nanosuspension were indicative of conversion of crystalline drug to amorphous form. The same results were observed with DSC study.

Scanning electron microscopy

The SEM of optimized batch shows the crystalline forms were converted into amorphous form which was an agreement with the results of DSC and XRD studies. The conversion of crystalline to amorphous nature of the drug is the main reason for increased solubility and dissolution along with improved wettability due to presence of soluplus. Figure 4.

In vitro dissolution studies

The drug release behavior of different batches of prepared nanosuspension and pure drug is shows in

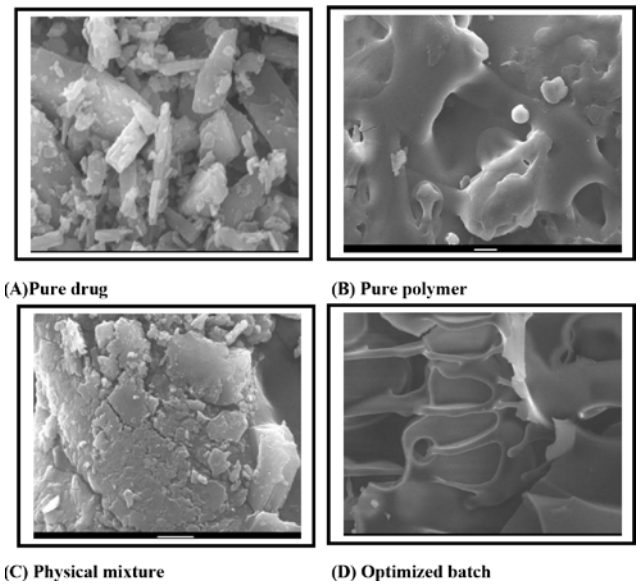


Figure 4: SEM of pure drug, pure polymer, physical mixture and optimized batch.

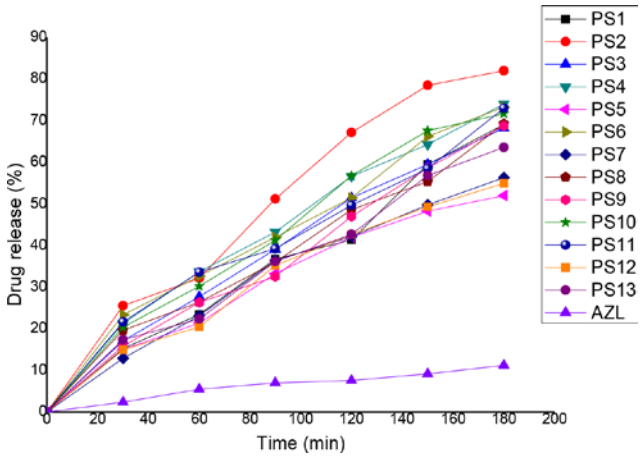


Figure 5: *In-vitro* drug release of pure drug and all 13 batches of nanosuspension.

Figure 5. Drug release for all 13 batches was in ranges of 51.98%-81.99% for 180 min. The pure drug exhibited the *in vitro* release of about 11.23 % for 180 min. At polymer concentration of 1% with sonication time 15 min, the batch PS2 shows higher dissolution rate i.e. 81.99% as compare to other batches. Batch PS5 containing 0.1% of polymer concentration and 20 min of sonication, it shows only 51.98 % drug release. So, polymer concentration is mostly impact on drug release behavior of nanosuspension.

Stability study

The results show that temperature has impact on accretion of nanosuspension and at room temperature accretion was greater as compared to refrigeration. We conclude that the particle size increased with increasing in temperature. The aggregation of the particles caused the rise in particle size at room temperature. Another factor could be the Ostwald ripening caused by temperature variations in the room. Table 3.

Table 3: Particle size, PDI and % drug release after stability.

Sr. No.	Evaluation Parameter	Initial	After 90 days	
			At 5°C±3°C	At 25°C
1	Particle size	168± 10	170±9	250±12
2	PDI	0.314±0.02	0.315±0.3	0.623±0.4
3	% drug release	81.99% ± 2.55	80% ±2.10	73% ±1.56

OPTIMISATION

To determine the impacts of independent factors (X_1, X_2) on dependent variables, a 3^2 response surface methodology was used (Y_1,Y_2). 2D (Figures 6a and 7a) and 3D counter plots were used to examine the effects of independent variables (Figures 6b and 7b). The three-dimensional (3D) response surface graph is extremely helpful in determining the main and interaction effects of independent variables Particle size (nm) and DR were chosen as independent variables for this investigation, whereas % polymer concentration (X_1) and sonication time (X_2 min) were chosen as dependent variables. The particle size ranged from 168 to 850 nm, and the DR ranged from 51.98 to 81.99 % in all 13 experimental runs, as shown in Table 1. Polynomial equations and counterplots are used to study the mathematical relationship between the dependent and independent variables. The R^2 values for the quadratic model (Y_1) response and the linear model (Y_2) response were 0.7523 and 0.7299, respectively, indicating satisfactory match (Table 4). The following equations were found for the EE (Y_1) and DR (Y_2) responses.

$$Y_1 = +388.90 - 170.67x_1 - 71.00x_2 + 162.86x_1^2 - 97.14x_2^2 + 150.00x_1x_2 \quad (3)$$

$$Y_2 = +67.37 + 10.25x_1 - 1.41x_2 \quad (4)$$

Positive and negative values in the above equations represent synergistic and antagonistic effects, respectively. Table 5 shows the ANOVA results for model Y_1 and Y_2 response. The independent variables $x_1, x_2, x_1^2; x_2^2$ and x_1x_2 influenced particle size (Y_1), according to the quadratic equation (2). Similarly,

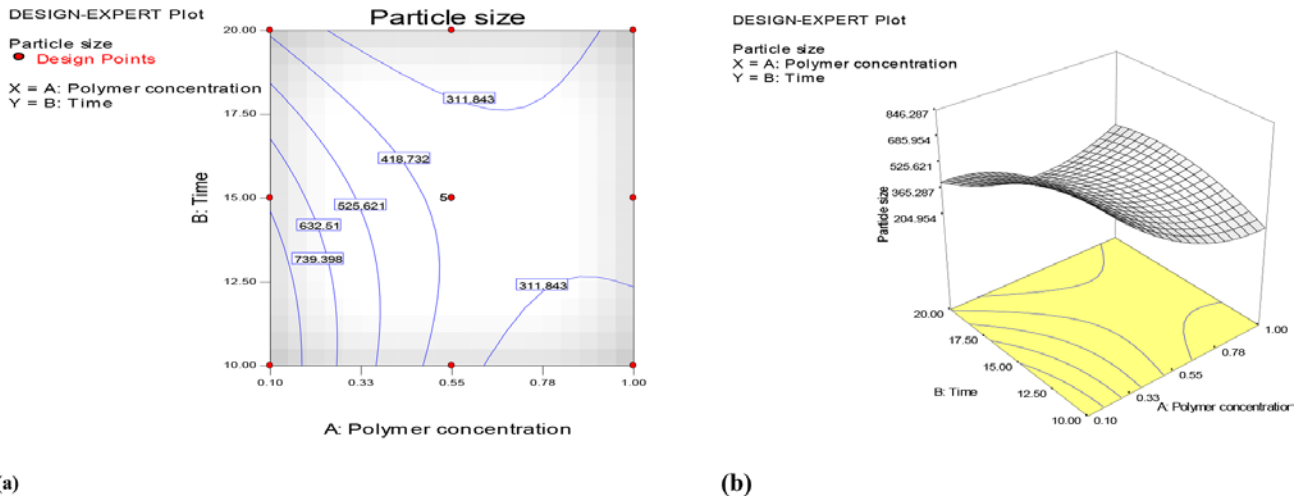
Table 4: Summary of results of regression analysis for responses Y_1 and Y_2.						
Source	**Std. Dev.**	**R-Squared**	**Adjusted R-Squared**	**Predicted R-Squared**	**PRESS**	**Remarks**
Response Y_1						
Linear	170.2391	0.414308	0.297169	−0.33988	663002.3	
2FI	149.0017	0.596191	0.461588	−0.39977	692637.8	
Quadratic	132.3294	0.75228	0.575337	−1.42943	1202135	Suggested
Cubic	48.52657	0.976205	0.942893	−1.49367	1233924	
Response Y_2						
Linear	4.874036	0.729921	0.675906	0.415009	514.5611	Suggested
2FI	5.123114	0.731451	0.641935	−0.28554	1130.765	
Quadratic	4.662597	0.826992	0.703415	−0.05962	932.043	
Cubic	5.044136	0.855371	0.65289	−11.1979	10729.35	

Regression equations of the fitted models

$$Y_1 = +388.90 - 170.67x_1 - 71.00x_2 + 162.86x_1^2 - 97.14x_2^2 + 150.00x_1x_2$$

$$Y_2 = +67.37 + 10.25x_1 - 1.41x_2$$

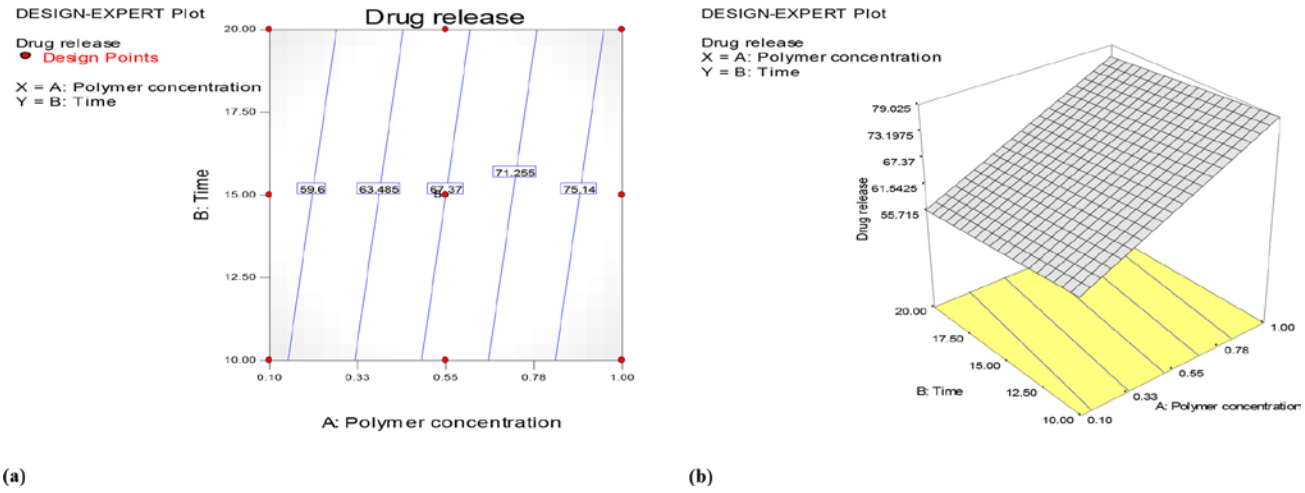
Table 5: ANOVA of models for Y_1 and Y_2.						
Source	**Sum of Squares**	**DF**	**Mean Square**	***F* Value**	**Prob > F**	**Remarks**
Model for Y_1						
Model	372244.8	5	74448.97	4.251538	0.0426	significant
	174762.7	1	174762.7	9.980126	0.0159	
	30246	1	30246	1.727251	0.2302	
	73256.91	1	73256.91	4.183463	0.0801	
	26060.72	1	26060.72	1.488243	0.2620	
	90000	1	90000	5.139607	0.0577	
Model for Y_2						
Model	642.0423	2	321.0211	13.51313	0.0014	Significant
	630.17	1	630.17	26.52651	0.0004	
	11.87227	1	11.87227	0.499754	0.4958	



(a) (b)

Figure 6: 2D contour plot (a) and 3D response surface plot (b) for particle size.

Table 6: Diagnostics case statistics for various response variables.							
Batch number	**Actual Value**	**Predicted Value**	**Residual**	**Batch number**	**Actual Value**	**Predicted Value**	**Residual**
For particle size				**For drug release**			
PS1	827	846.2874	-19.2874	PS1	54.91	58.52833	−3.61833
PS2	231	362.7586	-131.759	PS2	73.25	68.77667	4.473333
PS3	356	204.954	151.046	PS3	73.98	79.025	−5.045
PS4	850	722.4253	127.5747	PS4	56.32	57.12167	−0.80167
PS5	380	388.8966	-8.89655	PS5	69	67.37	1.63
PS6	168	381.092	-213.092	PS6	81.99	77.61833	4.371667
PS7	296	404.2874	-108.287	PS7	51.98	55.715	−3.735
PS8	267	220.7586	46.24138	PS8	72.99	65.96333	7.026667
PS9	425	362.954	62.04598	PS9	68.73	76.21167	−7.48167
PS10	415	388.8966	26.10345	PS10	69.22	67.37	1.85
PS11	425	388.8966	36.10345	PS11	63.55	67.37	−3.82
PS12	400	388.8966	11.10345	PS12	68.21	67.37	0.84
PS13	410	388.8966	21.10345	PS13	71.68	67.37	4.31



(a) (b)

Figure 7: 2D contour plot (a) and 3D response surface plot (b) for drug release.

the independent factors x_1 and x_2 altered the DR (Y_2) response, which likewise denotes a quadratic equation. These independent variables had substantial effects on particle size and DR at $P<0:05$. At $P<0:05$, both models were significant with F values of 2.20 and 13.51. Table 6 shows diagnostic case statistics with actual, expected, and residual values for various response variables. The prediction error was calculated by comparing the resultant experimental value to the expected value. Because the discrepancy between actual and projected values was smaller, the model was found to be strongly fit.[14]

CONCLUSION

The nanocrystals were made in thirteen distinct batches with variable polymer concentrations and sonication times utilising the novel amphiphilic carrier soluplus. The impacts of independent factors such as % polymer concentration (X_1) and sonication duration (X_2 min) on dependent variables such as particle size (Y_1 nm) and % drug release (DR) were optimised using a 3^2 response surface methodology (Y_2). The particle size, PDI, and zeta potential of AZL nanocrystals (PS2 batch) were found to be 168 nm, 0.314, and -22.72 mV, respectively. The presence of distinctive peaks in both the physical combination and the optimised nanosuspension at the same wave number indicates that there is no interaction between the medication and the polymer. According to XRD, the absence of a drug peak in the optimised nanosuspension indicates that the crystalline drug has been transformed to an amorphous form. Because there were no drug peaks in the optimised nanosuspension,

the crystalline drug had been transformed to amorphous form. The DSC research had the same results. *In vitro* dissolution of PS2 formulation and pure drug was 81.99% and 11.23%, respectively. From the present study we can conclude that the nanosuspension technique is an essential and useful technique for improving dissolution of poorly water-soluble drugs. The results obtained from solubility, *in-vitro* dissolution and interaction study describes that the drug formulating batches of nanosuspension technique shows the desired dissolution profile and increase solubility rates with no change in stability of drug.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AZL: Azilsartan medoxomil; **PDI:** Polydispersity index; **ARB:** Angiotensin II receptor blocker; **FT-IR:** Fourier transform infrared spectroscopy; **XRD:** X-ray powder diffraction; **DSC:** Differential scanning calorimetry; **SEM:** Scanning electron microscopy.

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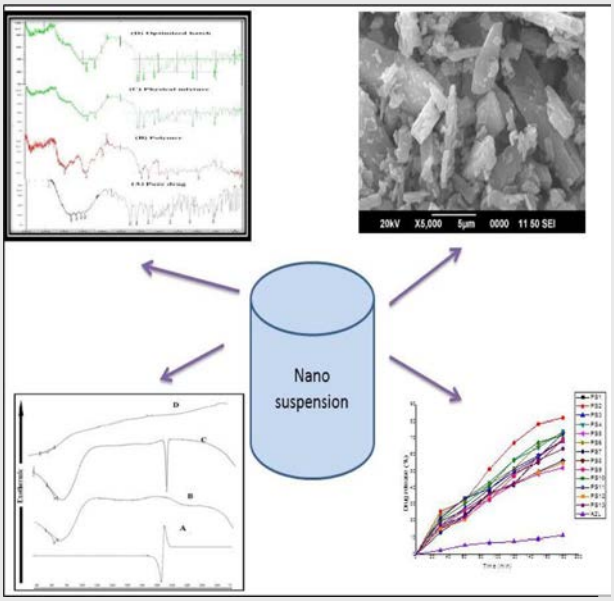
PICTORIAL ABSTRACT



SUMMARY

Azilsartan medoxomil (AZL) is an orally active nonpeptide angiotensin II receptor antagonist with less water solubility and oral bioavailability. We used a probe sonication approach to create nanocrystals. The impacts of independent factors such as % polymer concentration (X1) and sonication duration (X2 min) on dependent variables such as particle size (Y1 nm) and % drug release (DR) were optimised using a 3^2 response surface methodology (Y2). The results obtained from solubility, *in-vitro* dissolution and interaction study describes that the drug formulating batches of nanosuspension technique shows the desired dissolution profile and increase solubility rates with no change in stability of drug.

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