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BOX BEHNKEN MODEL-BASED LIQUISOLID COMPACT TECHNIQUE FOR THE IMPROVEMENT OF SOLUBILITY AND DISSOLUTION RATE OF AZELNIDIPINE

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The present investigation deals with improving solubility and dissolution rate, thereby achieving greater bioavailability and absorption by the Liquisolid Compact Technique. The significant therapeutic efficacy of Azelnidipine for the therapy of hypertension was attained. Liquisolid compact is the most effective technique based on the incorporation of suitable non-volatile liquid for the improvement of solubility. The liquid medicament is transformed into a free-flowing compacted material by adding a carrier and coating agent. The compatibility was confirmed with FTIR and thermal analysis with DSC. PEG 400 was chosen to indicate the highest solubility. The optimization was performed with Box-Behnken design using Design of Expert software considering the extent of carrier, coating, and superdisintegrant as independent factors and disintegration, dissolution was the dependent factor. The Box-Behnken design was implemented which predicted 12 runs and ANOVA with p-values was 0.0285 and 0.0444 for dependable parameters such as disintegration time and dissolution respectively. The Response surface methodology was retrieved with the 2-D Contour and 3-D plots along with ANOVA. The F2 was an optimized batch with an excellent flowability index and disintegration time of 3.01 min. The medicaments within 30 minutes with a higher dissolution rate of 99.38 %. The F2 batch qualified for stability testing when retained at 40 ^{0} C and 75 % RH. The superior improvement in solubility and dissolution level of AZN was achieved with the Liquisolid Compaq technique

Keywords:*Azelnidipine, Hypertension, Liquisolid Compact, Aerosil 200, Solubility enhancement*

INTRODUCTION

One of the greatest challenges in the pharmaceutical industry toward the progress of dosage forms is the limited solubility of an active ingredient[1]. Such active molecules elicited poor bioavailability and ultimately resulted in minimal therapeutic efficacy. Bioavailability at the site of action is the key parameter for any therapeutic molecule to exert its action[2]. The bioavailability of any medicament mainly depends on the absorption in the gastrointestinal tract, colon, and other parts of the body. The active ingredients, which showed good solubility and dissolved in the body fluids, are considered good candidates. The prompt solubility and dissolution rate is the GIT are of great concern for solid oral drug delivery. Additionally, presystemic metabolism and intestinal permeability are the key factors that determine the oral bioavailability of the active ingredients[3]. The rate-determining phase in the progression of drug absorption and bioavailability is dissolution.

The newly invented therapeutic molecule possesses greater lipophilicity intending to cross the GI barrier and thereby exerts the therapeutic action. Approximately 70-80 % of

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new chemical entities and 40-50% of the existing molecules showed poor solubility[4]. Out of them, only 8-10% of the medicament showed good solubility and permeability characteristics, hence they don't need any solubility enhancement technique [5]. The structural and chemical alterations of these molecules result in a tedious, time-consuming, and unaffordable process from the patient's point of view [6]. The unrivaled circumstances of Lipinski's "Rule of Five" prevent those substances from providing therapeutic efficacy [7]. The active ingredients with less than 100 mg/ml of a molecule are regarded as having poor water solubility [8]. Furthermore, the BCS standard for poorly soluble molecules explored that it cannot be dissolved in 250 ml of solution within a pH of 1-7.4 at 37 ±0.5 ^{0} C [9].

Spires first invented the technique for the progress of solubility and dissolution rate known as the Liquisolid Compact process. This system uses a non-volatile solvent (NVS) and liquid medication with a lipophilic moiety is created from the hydrophobic powder. By adding carrier and coating ingredients, liquid medications are additionally transformed into spontaneously flowing, compact powder. The carrier agents' surfaces absorb the liquid load, and adding coating agents enhances the powder's flow properties. According to the Liquisolid Compact system, superdisintegrants and lubricants are added to tablets to create quick-release formulations [10]. By increasing the contact with solid particles with NVS and increasing surface area, to obtain better solubility and dissolution of poorly soluble active components [11].

Solid orals are still at the top of the market despite of invention of several new dosage forms. These are highly popular due to offering unit dose, greatest accuracy, stability, safety, economical, higher patient comfort, and compliance [12]. Dissolution is the speed-restraining period for all drugs administered orally. To overcome such hindrances, it is necessary to progress the solubility and thereby dissolution rate of poorly soluble molecules [13].

Azelnidipine (AZN) is classified as a dihydropyridine calcium channel blocker (CCB) and suggested for the therapy of thrilling upsurge in blood pressure and other cardiovascular complications. AZN is better than rest CCB agents which diminishes the blood pressure with minimal rising heart rate. AZN is an extremely lipophilic compound recognized with a log P value of 5.12 and hence practically insoluble in water (0.00082 mg/mL). The present investigation focused on enhancing the solubility, and dissolution rate and thereby accelerating the absorption, bioavailability, and therapeutic efficacy of AZN by developing Liquisolid tablets which are administered orally [14 15].

MATERIALS AND METHODS

Azelnidipine was gifted by Ajanta Pharma, Aurangabad. Microcrystalline cellulose, and cross carmellose sodium were bought from Loba Chemicals, Mumbai. Aerosil 200 was bought from Signet Chemicals, Mumbai. The remaining chemicals and reagents utilized were of analytical grade only.

Organoleptic Characteristics, Loss on drying (LOD), and Melting point

The available powder sample of AZN was checked for its organoleptic properties such as color, nature, and odor, if any. An accurately weighed powder of 1 g was kept in a previously dry petri dish in a hot air oven (Remi Lab, India) at 105^0 C for about 2 hr., and after that powder sample was reweighed to determine loss of content during drying. Moreover, a digital melting point apparatus (Equiptronics Analytica LLP, Mumbai) was utilized to check the melting point of AZN [16].

Selection of non-volatile solvent

Assessment of the best suitable NVS for improvement of solubility of AZN was carried out in Tween 20, Tween 80, Span 80, Polyethylene glycol 200 and 400 grades, and propylene glycol, etc. The therapeutic dose of 8 mg of AZN was carefully transferred into several test tubes comprised of non-volatile solvents. These test tubes were stirred on the vortex mixer (Remi Lab, India) and further analyzed spectrophotometrically at 241 nm (Shimadzu Japan) [17].

Estimation of load factor

The manufacturing of tablets mainly depends on the free-flowing appearance of the powder blends. Hence, the efficiency of these powder blends to adsorb the non-volatile liquid

was estimated. The critical factors that decide the flowability of powder blends depends on the viscosity of NVS, quantity of carrier, and coating agents to make the powder blend easily flowable and consolidated. The liquid load factor was premeditated from the succeeding equations [18.]

$R = Q/ q$ ……1

$Lf = \Phi_{ca} + \Phi_{co} \quad x\ 1/R$ ……2

$Q = W/L_f$ ……3

In the above equations, R stands for excipient ratio, Q and q: for the weight of carrier and coating materials, Lf is the liquid load factor, W is the weight ratio of the liquid medicament, Φ_{ca} and Φ_{co} are the material quantity of carrier and coating agents respectively.

Drug-excipient Compatibility studies

The contacts between the AZN with carrier and coating agent were investigated with FTIR (IRAffinity-1s, Shimadzu). The precisely balanced extent of AZN with formulation constituents (MCC and Aerosil 200) as well as the Liquisolid Compact mixture was categorized for estimation of compatibility. The blend was exposed for scanning from 400 to 4000 cm^{-1} [19].

DSC Study

The thermal investigation of drug and formulation ingredients were analyzed with Differential scanning calorimetry (DSC) (Mettler Toledo India Pvt. Ltd Mumbai) in a series of 50^0 C to 350^0 C by applying the heat with the velocity of 10^0C/min under the influence of nitrogen flowing rate of 10 ml/min[20].

Optimization

The ultimate aim of finished product is to achieve greater therapeutic efficacy, safety and free from any potential errors. This can be attainable with quality-by-design (QbD) approach which is an organized progress of dosage form without any errors and toxicity. The prime elements of QbD is the critical quality attributes (CQA) which was disintegration time along with dissolution for the tablets. For the implementation of QbD, the Design of Experiment (DoE, Statease, Version 13) was utilized with 3-independent and 2-dependent parameters. The Box-Behnken design was best suited for the optimization which predicted 12 runs [21.]

Analysis of powder characteristics

The powder mixtures were characterized for their flowing nature by bulk density (Electronics India), tapped density, Carr's index, Angle of repose, and Hausner's ratio [22].

Development of Liquisolid tablets of AZN

The critical parameter in the designing and development of the Liquisolid compact technique is the final weight of the tablets. The transformation of liquid medicament into the free-flowing powder was completely based on the adsorption capability of the carrier and coating agent namely microcrystalline cellulose and Aerosil 200. Several proportions of these agents were initially tried to get the final weight.

Specifically, the volume of the AZN was shifted in the mortar succeeding accumulation of nominated NVS. Microcrystalline cellulose was built on the liquid. Aerosil 200 was mixed in the powder blends in their compressible form (Rimek Mini Press II, Karnavati Engineering Ahmedabad). Before compaction, cross carmellose sodium (CCS), and sodium steraryl fumarate (SSF) were mixed. The preparation ingredients are represented in Table 1 [23.]

Evaluation of post-compression Tablets

Weight variation test

The 20 tablets were elected unevenly and assessed precisely on precision balance (Contech India). Thereafter, the average was verified [24].

Crushing strength

The pressure applied on the tablet, until it breaks, was confirmed by the Monsanto hardness tester [25].

Friability

The tablet's extent corresponding to 6.5 g was taken and positioned in the friabilator (Electrolab India) with a velocity of 25 rpm for 100 turnings. The tablets were reweighed and the ratio of the friabilator was premeditated by deducting the weight of the original from the concluding weight [26].

Table 1: Constituents of Liquisolid Compact tablets of AZN.

Batch	AZN	PEG 400	MCC 102	Aerosil 200	Cross Povidone	SSF	Talc	Total
F1	8	16	250	60	17.5	3.5	3.5	359
F2	8	16	250	40	17.5	3.5	3.5	339
F3	8	16	260	50	17.5	3.5	3.5	359
F4	8	16	240	50	17.5	3.5	3.5	339
F5	8	16	250	40	10.5	3.5	3.5	332
F6	8	16	240	60	14	3.5	3.5	345
F7	8	16	260	40	14	3.5	3.5	345
F8	8	16	260	60	14	3.5	3.5	365
F9	8	16	250	60	10.5	3.5	3.5	352
F10	8	16	240	50	10.5	3.5	3.5	332
F11	8	16	240	40	14	3.5	3.5	325
F12	8	16	260	50	10.5	3.5	3.5	352

All the values are in mg

Disintegration time

The arbitrarily designated 6 tablets were retained in the disintegration apparatus (Electrolab India) at 37±0.5° C using 900 ml of simulated gastric fluid of pH 1.2. When the entire material screen out that time was considered [27].

In-vitro dissolution

For the estimation of in-vitro dissolution testing, the Paddle apparatus was selected. The dissolution media utilized in the Dissolution apparatus (Electrolab India) was phosphate buffer pH 7.4. The program was set in the apparatus with the paddle speed of 50 rpm, at 37±0.5° C. The samples were quiet for 5 minutes, diluted, filtered through a 0.41 µm membrane filter, and replaced with fresh buffer. Finally, samples were investigated by UV spectrophotometer at 241 nm in triplicates [28].

Drug content Uniformity

The tablets (20) were haphazardly picked and transformed into the powder. The equivalent extent of the tablet was dissolved with pH 7.4 phosphate buffer. The solution was filtered over a 0.41 µ membrane filter and investigated spectrophotometrically at 241 nm[29].

Stability study

The preferred batch was set aside at 40 ^{0}C and 75 % RH for around 90 days (Remi India). The samples were introverted at 30 days and assessed for drug content, disintegration, and dissolution time [30].

RESULT AND DISCUSSION

Result

Evaluation of organoleptic characteristics, LOD, and Melting point

The received sample of AZN was checked for color and found yellow crystalline powder having peculiar smell. The LOD value of the powder under the mentioned condition was found to be 0. 33%. The melting of powder initiated from 192 ^{0}C and completely melted at 195 ^{0}C. The melting point determination was performed with the intention of determination of drug identity and purity. Thus, originality of drug sample confirmed from these tests.

Scrutiny of NVS

The solubility of AZN was assessed initially in the distilled water and found that powder is practically insoluble. All the particles of AZN were not wetted due to the hydrophobic nature of the powder. Further, solubility was checked with several non-volatile solvents, and PEG 400 was found to be best. The solubility of AZN at room temperature was found to be 124µg/ml. The solubility estimation in several NVS was showed in Table 2. Hence, PEG 400 was chosen for the development of Liquisolid Compact.

Table 2: Solubility estimation of AZN.

Sr. No	Name of solvent	Solubility
1	Tween 20	124± 1.18 µg/ml
2	Tween 80	103± 1.21 µg/ml
3	Span 80	47± 0.87µg/ml
4	Polyethylene glycol 200	84 ± 0.67µg/ml
5	Polyethylene glycol 400	91±0.76 µg/ml
6	Propylene glycol	79±0.56 µg/ml

Compatibility study

The powder sample of AZN was subjected to the FTIR to evaluate the identity. The data retrieved from the spectrum is indicated in Fig.1. showed the availability of carbonyl group (C=O) stretching at 1693.50 cm^{-1}, C-N stretching at 1282.66 cm^{-1}, N-H bending at 1525.69 cm^{-1}, 1614.82 for C=C stretching, 1658.78 cm^{-1} for N-O. The presence of these functional groups recognizes the identity of AZN. The successful formulation should not have any interaction with the formulation components, which prevents the minimization of therapeutic efficacy. The spectrum and bands of AZN were not shifted after the incorporation of MCC and Aerosil 200. Hence, it was interpreted that AZN does not have any physical and chemical interactions with the formulation ingredients. The interaction studies with excipients were described in Fig.2 to 4 respectively.

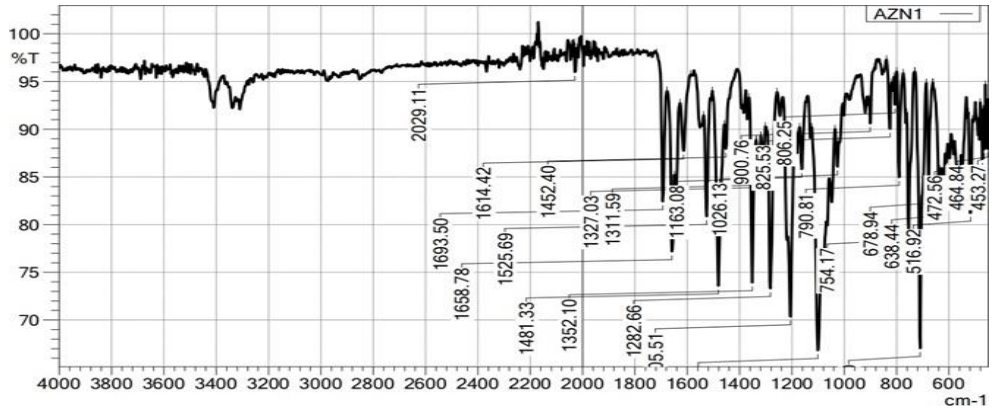

Fig. 1: FTIR Spectra of Azelnidipine.

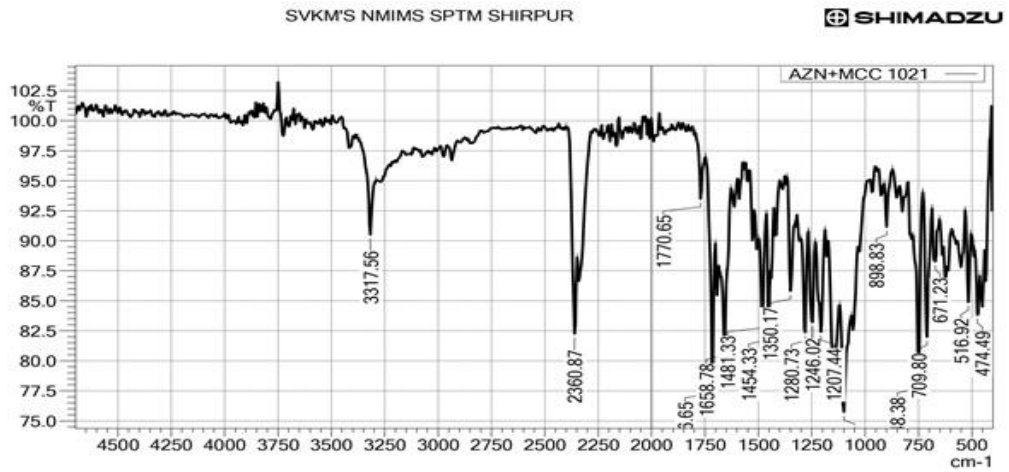

Fig. 2: FTIR Spectra of Azelnidipine and MCC 102.

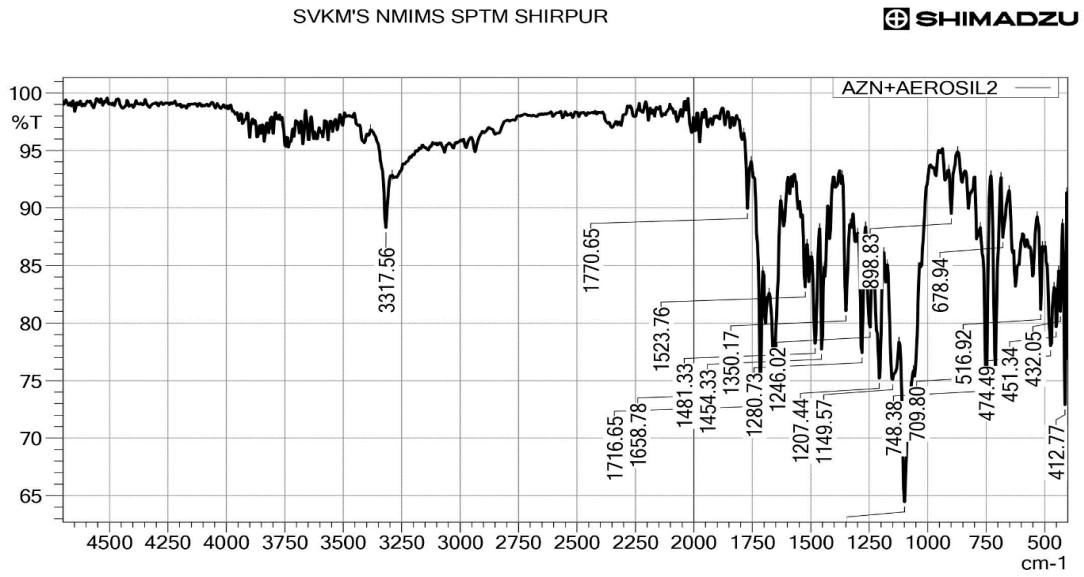

Fig. 3: FTIR Spectra of Azelnidipine and Aerosil 200.

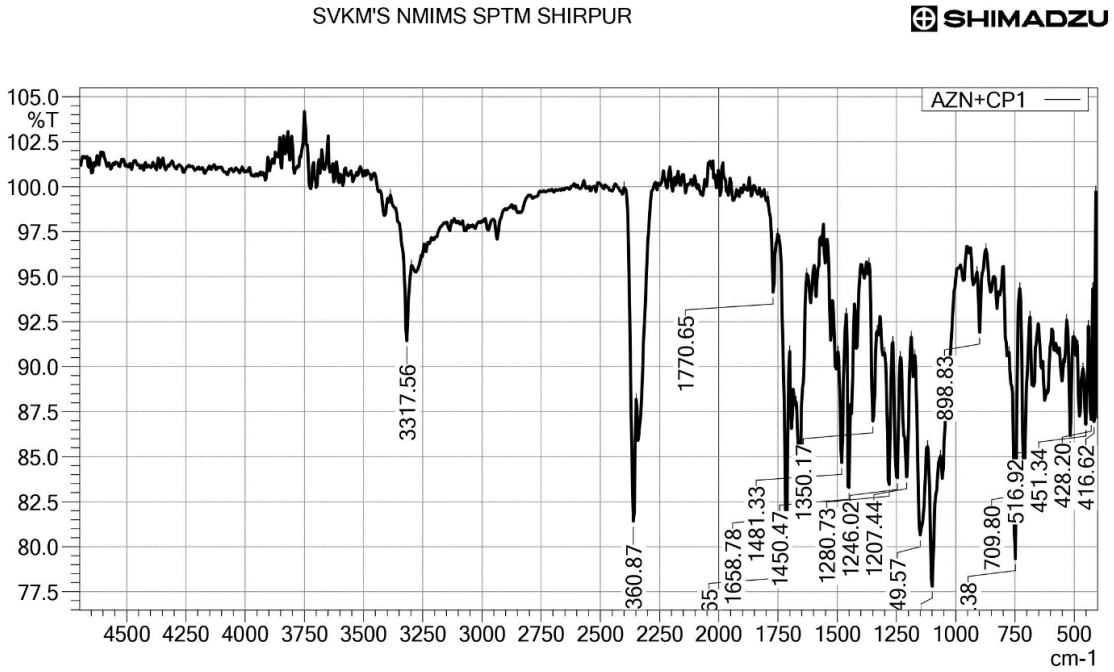

Fig. 4: FTIR Spectra of Azelnidipine and CP.

DSC analysis

The thermal estimation of AZN was carried out and the sharp intense peak originated at 191.82 ^{0}C and ended at 195.18 ^{0} C showed in Fig. 5. Thus, representing the crystalline nature of their upper endothermic peaks. The Liquisolid formulation comprised actives along with Tween 20 as well as carrier and coating agent. The physical mixture reflected displayed a melting point of 100.80 ^{0} C and complete melting at 102.08 ^{0} C. Hence, the melting point of the physical mixture shifted to the lower side by 93.1 ^{0} C showed in Fig. 6. Thus, the crystalline nature was shifted towards the amorphous by minimizing the sharp intensity. Azelnidipine was entirely dissolved in the Tween 20 which reflects complete miscibility.

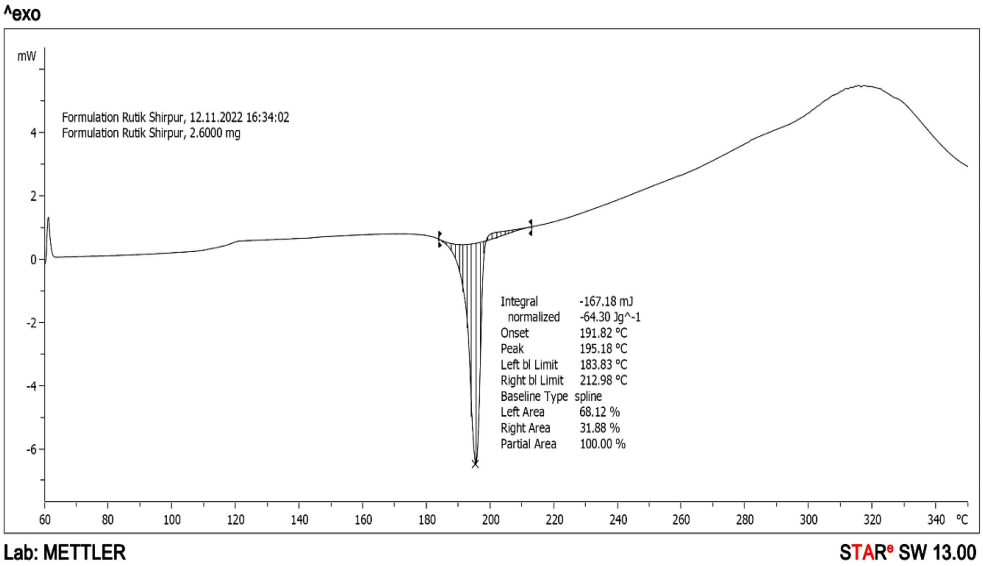

Fig. 5: DSC thermogram of pure AZN.

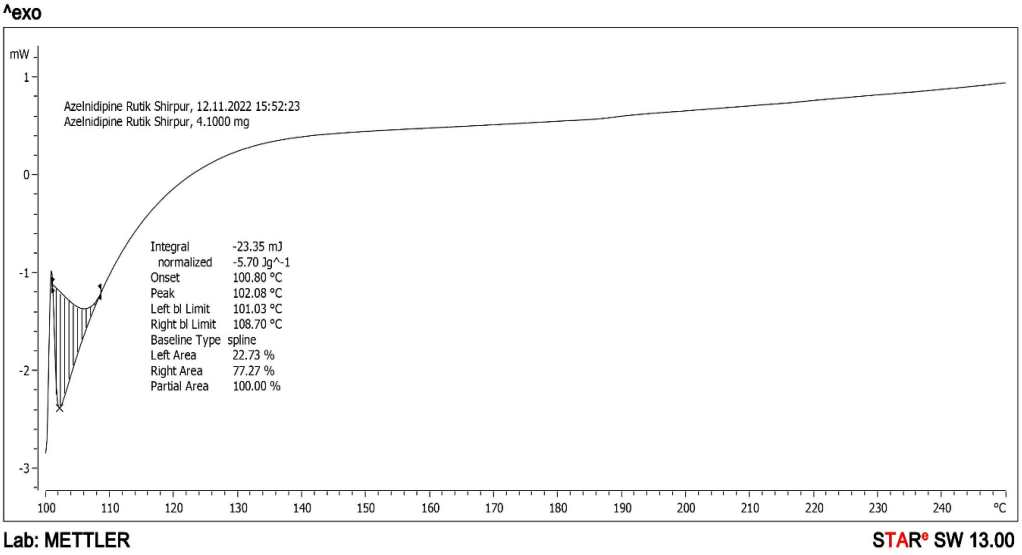

Fig. 6: DSC thermogram of AZN and formulation.

Optimization analysis

For the optimization analysis, the Design of Expert (DoE, Statease Version 13) software was implemented. There were 3-independent formulation parameters namely concentration of microcrystalline cellulose (X1), Aerosil 200 (X2), cross povidone (X3), and 2-dependent parameters such as disintegration time (Y1) and dissolution release (Y2). These 3-independent and 2-dependent parameters suggested Box-Behnken design (BBD) suited best for the processing of tablets. In the Design Expert software, MCC, Aerosil, and cross povidone were taken as independent factors with lower and higher limits based on the flowing nature of the powder blends. Hence, the final weight of the tablet varies. The BBD for AZN is illustrated in Table 3.

Table 3: The BBD for the optimization of AZN Tablets.

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:MCC 102	B:Aerosil 200	C:Cross Povidone	Disintegration Time	Dissolution
		mg	mg	mg	min	%
8	7	250	60	17.5	3.06	99.20
3	3	250	40	17.5	3.01	99.38
6	9	260	50	17.5	3.09	99.17
11	11	240	50	17.5	3.04	98.95
7	5	250	40	10.5	3.11	98.66
4	2	240	60	14	3.05	98.85
10	8	260	40	14	3.08	98.74
9	10	260	60	14	3.08	98.68
12	12	250	60	10.5	3.10	98.67
1	4	240	50	10.5	3.12	98.61
2	1	240	40	14	3.06	98.43
5	6	260	50	10.5	3.13	98.38

The dependable parameters such as disintegration time and dissolution time data were fitted for ANOVA and their model was found to be significant. The p-value for DT was found to be 0.0285 and for dissolution was 0.0394 displayed in **Tables 4 and 5** respectively.

The quadratic polynomial equation for disintegration time is mentioned below.

$DT = +3.10 +0.0137\ A +0.0038\ B -0.0325\ C +0.0025\ AB +0.0100\ AC +0.0150\ BC -0.0025\ A^2 -0.0275\ B^2 +0.0000\ C^2$.

In the above equation, the parameters A, B, and C were the concentration of MCC, Aerosil 200, and cross povidone respectively. The plus sign in this equation indicated the synergistic effect whereas the minus sign indicated the antagonistic effect. The terms AB, AC, and BC represented the combined value of independent parameters. The mean disintegration time was noted as 3.10 min and synergistic effects were showed by the concentration of MCC and Aerosil, whereas cross-povidone indicated antagonistic effects. The 2-D contour plots along with their 3-D surface response curve for disintegration time were showed in **Fig. 7** to 10 respectively.

Table 4: ANOVA for Quadratic model containing response 1: Disintegration Time.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0133	8	0.0017	13.25	0.0285	significant
A-MCC 102	0.0015	1	0.0015	12.10	0.0401	
B-Aerosil 200	0.0001	1	0.0001	0.9000	0.4128	
C-Cross Povidone	0.0085	1	0.0085	67.60	0.0038	
AB	0.0000	1	0.0000	0.2000	0.6850	
AC	0.0004	1	0.0004	3.20	0.1716	
BC	0.0009	1	0.0009	7.20	0.0748	
A^2	0.0000	1	0.0000	0.1000	0.7726	
B^2	0.0015	1	0.0015	12.10	0.0401	
C^2	0.0000	0				
Residual	0.0004	3	0.0001			
Cor Total	0.0136	11				

ANOVA for Quadratic model.

Table 5: ANOVA for Quadratic Model containing response Dissolution.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.02	8	0.1277	9.64	0.0444	significant
A-MCC 102	0.0021	1	0.0021	0.1595	0.7163	
B-Aerosil 200	0.0045	1	0.0045	0.3408	0.6004	
C-Cross Povidone	0.7080	1	0.7080	53.47	0.0053	
AB	0.0576	1	0.0576	4.35	0.1283	
AC	0.0506	1	0.0506	3.82	0.1455	
BC	0.0090	1	0.0090	0.6816	0.4696	
A^2	0.1830	1	0.1830	13.82	0.0339	
B^2	0.0210	1	0.0210	1.59	0.2969	
C^2	0.0000	0				
Residual	0.0397	3	0.0132			
Cor Total	1.06	11				

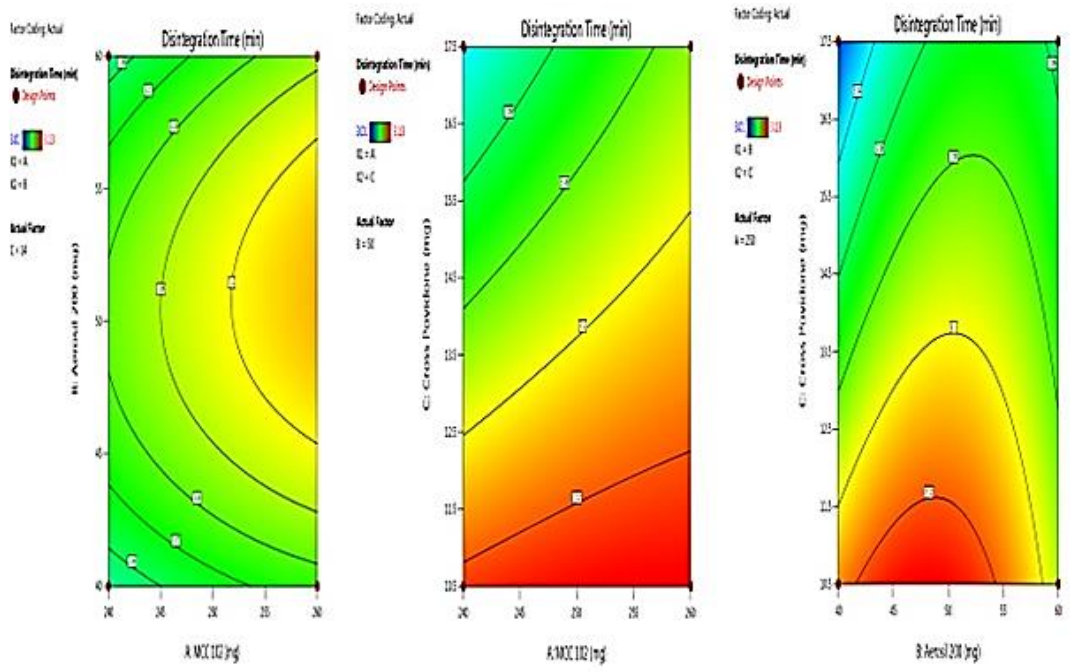

Fig. 7: 2-D Contour Plot DT.

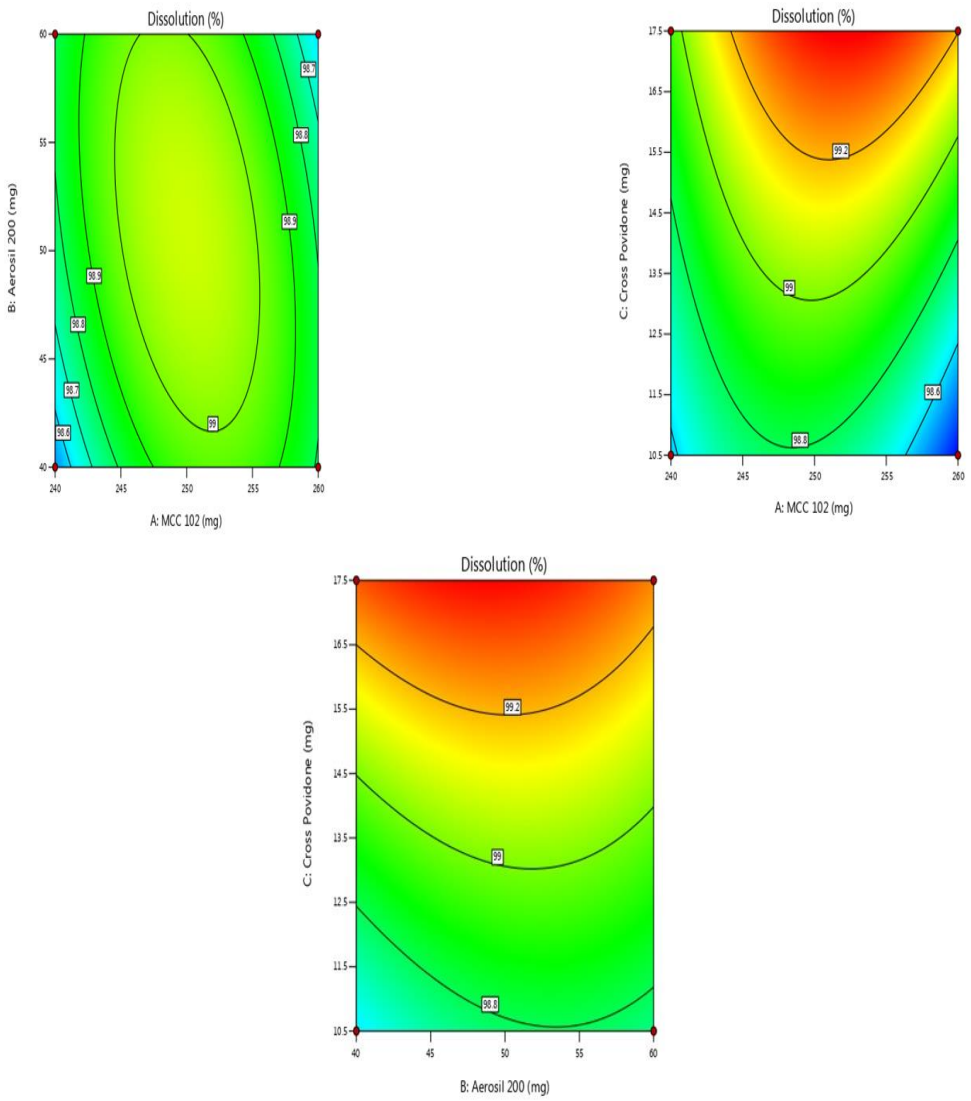

Fig. 8: 2-D Contour Plot for the Dissolution.

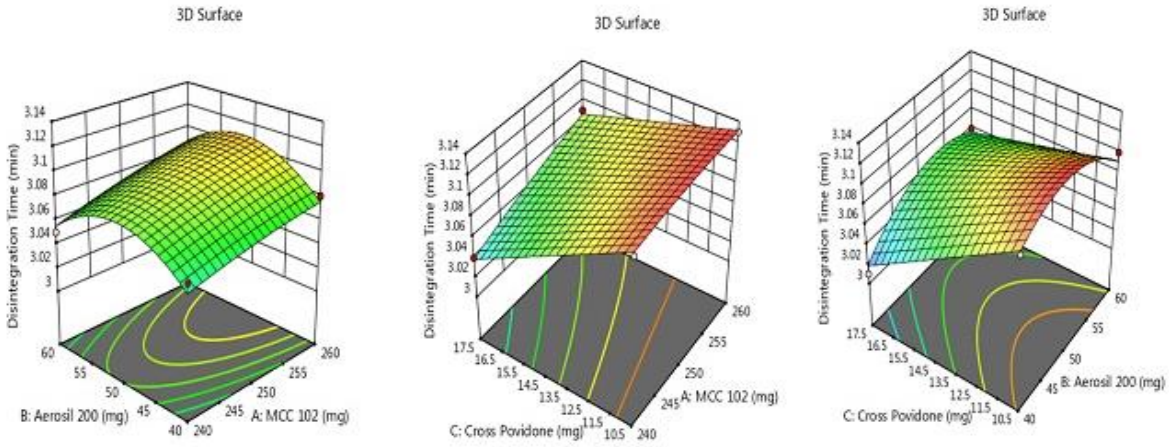

Fig. 9: 3-D Response Surface graph for DT.

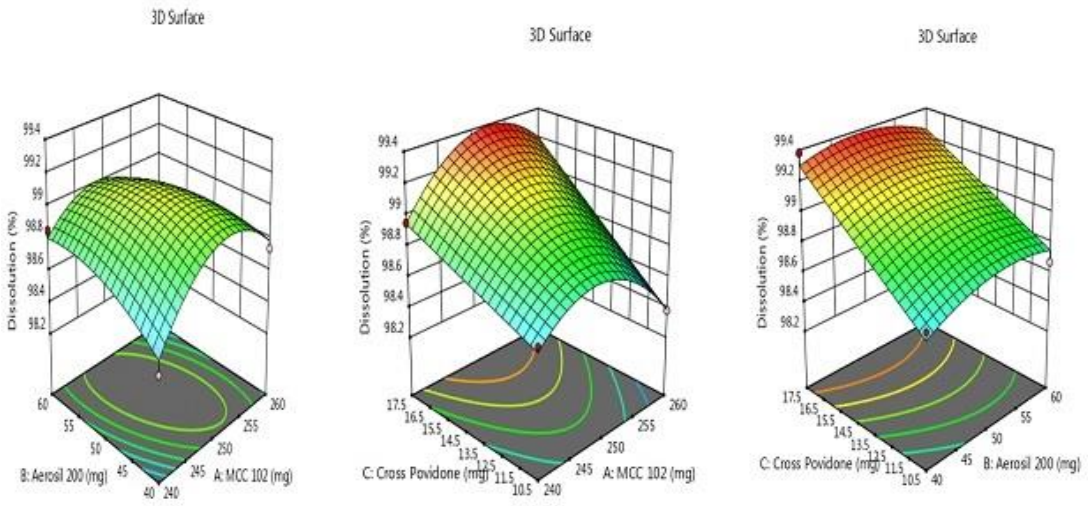

Fig. 10: 3-D Response Surface graph for Dissolution.

Similarly, the quadratic polynomial equation for the second dependable parameter known as dissolution is stated below.

Dissolution = +99.08 +0.0162 A +0.0238 B +0.2975 C -0.1200 AB +0.1125 AC +0.0475 BC –0.3025 A^2 -0.1025 B^2 +0.0000 C^2

In this equation, the synergistic equation was indicated by all the parameters. The combined term AB as well as the sum of square terms A and B predicted the antagonistic effects respectively. The average drug dissolved in the medium was found to be 99.08 %. The 3-D surface response curve along with their 2-D contour plots for dissolution was showed in Fig. 8 and 10 respectively.

Evaluation of the flowing nature of powder blends

According to the DoE model, 12 batches were generated and all were assessed for their flowing behavior parameters such as bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio. The formulation of the Liquisolid Compact Technique is dependent on the material quantity of the carrier and coating agent which transformed liquid medicament into free-flowing powder ready to compress. Initially, the non-volatile solvent quantity was finalized, and depending on the viscosity of the solvent, several trials of carrier and coating materials were tested. These powder blends were evaluated for their flowing characteristics and hence the minimum quantity was finalized. Moreover, depending on the adsorption potential of the carrier and coating agent which converts liquid medicament into freely flowable powder was calculated. There was no exact proportion of carrier and coating agent utilized during the Liquisolid Compact technique. In this work 4:1 ratio was most appropriate for carrier to coating agent.

Initially, several trials were performed for the evaluation of flow characteristics with an extent of 200 to 250 mg of carrier and coating agent. From this amount, it was noticed that a 3:1 proportion works best. Moreover, the material above 240 mg of carrier and 40 mg of coating agent showed good to passable flowing characteristics. When the carrier agent quantity taken was 250 mg and 40 mg of coating agent then all the batches showed good to excellent flowing characteristics were observed. Further, the rise in material quantity slightly excels the flowing nature of the powder blends. However, the desired results were achieved in the trial of 250 mg of carrier agent and 40 mg of coating agents, hence F2 was selected best amongst them relying on disintegration time and dissolution of the active agent.

The results are represented in Table 6. The bulk density of powder blends was found to be 0.18 to 0.24. The tapped density of powders was observed from 0.21 to 0.30. The Carr's index of powders was calculated and perceived in the series of 14.28 to 20.69 %. The angle of repose values was showed to be 22.79 to 31.48 and Hausner's ratio was estimated to be 1.17 to 1.26. The powder blends showed large variations in the flowing characteristics which was attributed due to their composition. The blends with more quantities of carrier agents showed excellent flowing characteristics than

moderate and low levels. The increase in the quantity of coating agent decreases the flow characteristics due to their extremely fluffy nature.

Estimation of AZN Tablets

The tablets of F1 to F12 were exposed for weight variation, hardness, friability, disintegration time, *in-vitro* dissolution release, and content uniformity. The entire batch passed the weight variation test according to the limits prescribed for 350 mg tablets according to the Indian Pharmacopoeia. The hardness was verified with a Monsanto hardness tester and found in the series of 4.4±0.06 to 4. 7 ± 0.10 kg/cm^2. The slight variations in the hardness for different batches were attributed to the variation in the amount of materials. The friability was assessed using the Roche friabilator and detected in the range of 0.47±0.17 to 0.54±0.32 %. Similarly, the friability of tablets is influenced by the hardness, hence little difference was observed during the estimation of friability. The disintegration time of 3.03±0.14 to 3.13±0.16 min was noticed. The alterations in the disintegration were observed due to the variable concentration of superdisintegrants namely cross povidone. Tablets comprised of 17.5 mg of cross povidone have found the least disintegration time than with 14 mg and 10.5 mg of cross povidone. The content uniformity of all batches was witnessed in the series of 98.51±0.70 to 99.38±0.90 %. The outcomes are represented in **Table 7**.

Table 6: Flowing features of powder blends of AZN.

Batch	Bulk density	Tapped density	Carr's index (%)	Angle of Repose (Ɵ)	Hausner's ratio
F1	0.23±0.20	0.27±0.26	14.81±0.38	25.57±0.46	1.17±0.07
F2	0.22±0.24	0.26±9.23	15.38±0.34	26.82±0.44	1.22±0.04
F3	0.23±0.18	0.27±0.29	14.81±0.44	25.64±0.39	1.22±0.09
F4	0.24±0.21	0.29±0.26	17.24±0.36	28.72±±0.37	1.16±0.11
F5	0.23±0.16	0.28±0.32	17.85±0.30	28.97±0.40	1.2±0.14
F6	0.21±0.23	0.25±0.22	16±0.37	27.46±0.42	1.19±0.08
F7	0.18±0.20	0.21±0.28	14.28±0.41	25.72±0.36	1.16±0.05
F8	0.19±0.16	0.23±0.31	17.39±0.38	27.88±0.41	1.21±0.13
F9	0.23±0.14	0.27±0.34	14.81±0.28	26.14±0.45	1.19±0.15
F10	0.21±0.20	0.26±0.24	19.23±0.32	30.58±0.50	1.19±0.20
F11	0.23±0.22	0.28±0.28	17.85±0.37	28.34±0.48	1.21±0.16
F12	0.22±0.19	0.26±0.33	15.38±0.39	26.96±0.42	1.23±0.18

All values are n= ±3.

Table 7: The estimations of AZN Liquisolid Tablets.

Batch	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration (min)	Content uniformity (%)
F1	359±0.97	4.6±0.06	0.53±0.29	3.06±0.10	98.67±0.86
F2	339±0.78	4.4±0.11	0.49±0.18	3.01±0.16	99.46±0.70
F3	359±0.93	4.5±0.09	0.51±0.34	3.09±0.14	99.24±0.94
F4	339±0.69	4.4±0.06	0.54±0.24	3.04±0.12	99.04±0.80
F5	332±0.76	4.4±0.04	0.54±0.32	3.11±0.08	99.25±0.88
F6	345±1.07	4.6±0.18	0.48±0.20	3.05±0.14	98.72±0.68
F7	344±0.95	4.6±0.15	0.47±0.17	3.08±0.20	99.21±0.95
F8	365±0.68	4.5±0.12	0.50±0.20	3.08±0.06	98.84±0.66
F9	352±0.75	4.7±0.10	0.45±0.27	3.10±0.10	99.15±0.67
F10	332±0.54	4.5±0.07	0.51±0.19	3.12±0.16	99.38±0.90
F11	325±0.72	4.5 ±0.15	0.50±0.28	3.06±0.12	98.96±0.77
F12	352±0.59	4.5±0.05	0.51±0.26	3.13±0.07	99.23±0.70

All values are n =3 ±SD.

In-vitro drug release of AZN Liquisolid Tablets

The drug-released profile from the LCT tablets was accomplished with an in-vitro type II dissolution apparatus. The LCT was completely liberated within 45 min indicating an immediate release profile and from that, it was concluded that the dissolution was rapid. Among the 12 batches, the highest amount of drug release was noted with F2 indicating 99.38 % within 30 min. Furthermore, the F1 batch was also completely released in 30 minutes with 99.20 %. Similar to F1 and F2 batches, F4 to F6 were also liberated within 30 min with the cumulative drug release of 98.95 % and 98.85 % respectively. The batches F3 and F5 have showed the drug release of 99.17 % and 98.66 % within 40 min. The greater amount of drug released from batches F1 and F2 was credited to the superior extent of cross-povidone in their composition, which released the drug quickly.

The drug released from F7 to F12 was found to be 98.74 %, 98.68 %, 98.67 %, 98.61%, 98.43 %, and 98.38 % respectively within 30 min, except for the batches F9, F10, and F12 that were liberated within 40 min. The difference in all batches was similar to the varying concentration of composition and greater hardness was responsible for slower release of the medicament from the tablets. The release was showed in Fig. 11 and 12 respectively. The in-vitro dissolution studies were carried out for the marketed tablet and compared with the optimized batch. The release of drugs from the F2 batch was quicker than marketed tablets. Approximately 99.38 % of actives were discharged within 25 min from the F2 batch. Comparatively, the marketed tablet was released entirely after 75 min with a cumulative drug release of 92.89 %.

Accelerated Stability testing

The optimized batch F1 was tested according to the ICH guidelines under 40 ^{0} C at 75 % relative humidity maintained in the stability chamber (Remi, Mumbai, India). The outcomes are represented in **Table 8**.

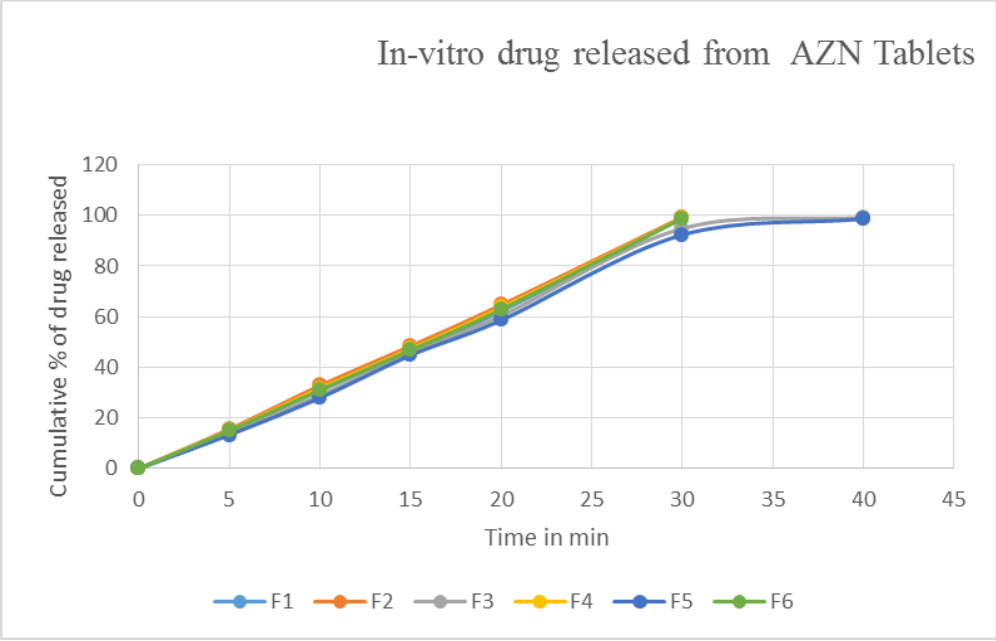

Fig. 11: In-vitro drug released profile of F1 to F6 of LC.

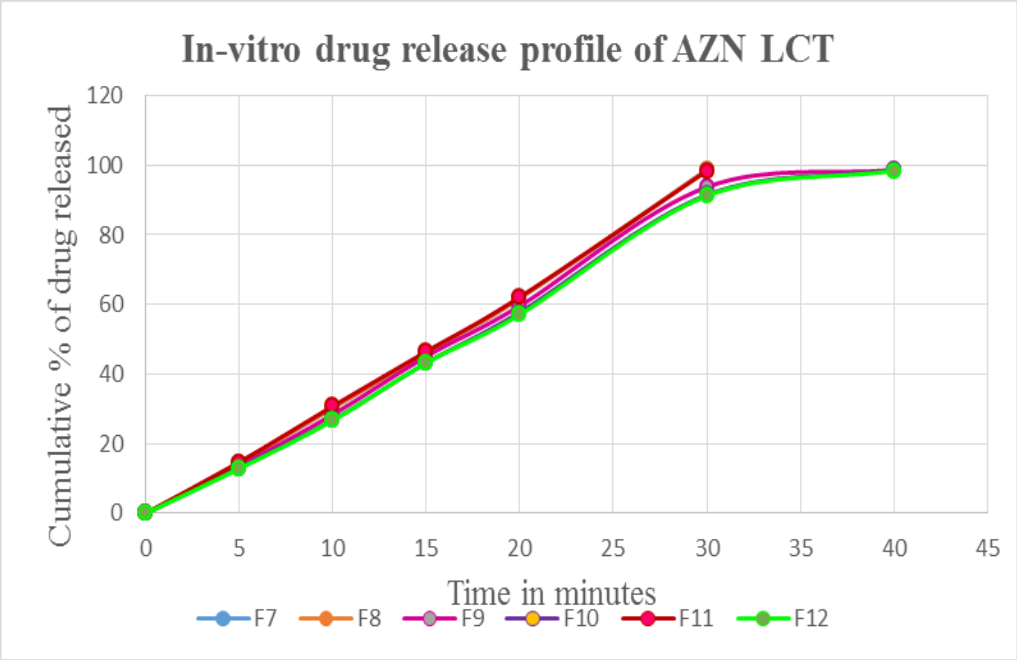

Fig. 12: In-vitro drug released profile of F7 to F12 of LCT.

Table 8: Stability assessment of an optimized batch F2.

Parameters	Initial	After 1 month	After 2 month	After 3 month
Hardness	4.4±0.11	4.4±0.36	4.2±0.18	4.1±0.22
Friability	0.49±0.18	0.50±0.30	0.52±0.42	0.54±0.56
Disintegration	3.01±0.14	3.01±0.26	2.58±0.32	2.56±0.44
Content uniformity	99.46±0.70	98.70±1.15	98.38±0.89	98.15±0.76

All values are n= ±3.

Conclusion

Azelnidipine is widely recommended for the therapy of hypertension. The poor solubility and bioavailability restricted the therapeutic efficacy. Hence, solubility and dissolution rate were enhanced with PEG 400 as a non-volatile solvent using the Liquisolid Compaq technique. Box-Behnken design provided a randomized trial with minimum possible runs for the formulation and evaluation of LCT. The batch F2 was nominated owing to flowing characteristics, lowest disintegration time, and greater dissolution release within 30 min. The LCT is a cost-effective and rapid method compared with other solubility enhancement techniques. Hence, it was concluded that LCT is beneficial for improving the solubility and dissolution of poorly water-soluble drugs or BCS-II drugs.

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نشرة العلوم الصيدلية
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إستخدام نموذج Box Behnken الإحصائى لتحسين قابلية الذوبان ومعدل ذوبان الأزيلنيديبين وذلك فى تقنية السوائل الصلبة المضغوطة

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يتناول هذا البحث تحسين معدل الذوبان والذوبان، وبالتالي تحقيق قدر أكبر من التوافر البيولوجي والامتصاص بواسطة تقنية . Liquisolid Compact وذلك لتحقيق الفعالية العلاجية الكبيرة للأزيلنيديبين في علاج ارتفاع ضغط الدم. و يعتبر Liquisolid Compact هو الأسلوب الأكثر فعالية الذي يعتمد على دمج سائل غير متطاير مناسب لتحسين القابلية للذوبان. وعن طريق هذه التقنية يتم تحويل الدواء السائل إلى مادة مضغوطة تتدفق بحرية عن طريق إضافة مادة حاملة ومادة مغلفة . وتم تأكيد التوافق باستخدام تقنية الأعة تحت الحمراء (FTIR) والتحليل الحراري التوافقى باستخدام (DSC). وتم اختيار PEG 400 للإشارة إلى أعلى قابلية للذوبان. وقد تم إجراء التحسين باستخدام تصميم Box-Behnken باستخدام برنامج Design Expert مع الأخذ في الاعتبار مدى الناقل والمادة المغلفة والتفكك الفائق كعوامل مستقلة والتفكك، وكان الذوبان هو العامل التابع . و تم تنفيذ تصميم Box-Behnken الذي تنبأ بـ ١٢عملية تشغيل وأعطى التحليل الإحصائى ANOVA قيم P وهى ٠,٠٢٨٥ و٠,٠٤٤٤ للمعاملات التي يمكن الاعتماد عليها مثل وقت التفكك والذوبان على التوالي. وتم استخدام منهجية سطح الاستجابة باستخدام المخططات ثنائية الأبعاد وثلاثية الأبعاد جنبًا إلى جنب مع ANOVA كانت F2 عبارة عن صيغة مُحسّنة ذات مؤشر سيولة ممتاز ووقت تفكك قدره ٣,٠١ دقيقة. وكانت الصيغة المحضرة تعطى خلال ٣٠ دقيقة معدل ذوبان أعلى يبلغ ٩٩,٣٨%، وكانت الصيغة F2 مؤهلة لاختبار الثبات عند الاحتفاظ بها عند درجة حرارة ٤٠ درجة مئوية و٧٥% رطوبة نسبية، وتم التوصل إلى تحقيق التحسن الفائق في مستوى الذوبان لـ AZN باستخدام تقنية Liquisolid Compact