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Desıgn Optımızatıon and Evaluatıon of Mesoporous Sılıca Based Lıquısolıd Blends of Azelnıdıpıne

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Abstract:

Azelnidipine is a calcium channel inhibitor widely utilized for the management of hypertension. The therapeutic benefits are restricted due to high lipophilicity. The recent work focused on the enhancement of solubility dissolution rate and bioavailability of Azelnidipine by the Liquisolid Compact technique. One of the best solubility enhancement techniques for BCS-II potent molecules is the Liquisolid Compaq technique. The hydrophobic active ingredient is converted into the liquid medicament by adding a non-volatile solvent. Furthermore, the freely flowable and compressible powder blends were accomplished by the amalgamation of adsorbents. The highest solubility of Azelnidipine was observed in PEG 400. The drug-excipient interactions were checked with FTIR and DSC. The screening was performed with the Design of expert software with MCC 102 (X1), Parteck SLC (X2), crosspovidone (X3) as independent factors and disintegration (Y1) dissolution release (Y2) as dependable factors with 12 trial runs. The ANOVA was applied with a polynomial quadratic model with response surface methodology. The optimized batch F5 indicated excellent flowability characteristics, the least disintegration time (4.05 min), and the greatest dissolution release (99.31%) owing to the greatest adsorption capacity and surface area of mesoporous silica.

Keywords: Azelnidipine, Hypertension, Liquisolid Compact, Mesoporous Silica, Solubility enhancement.

Introduction

Hypertension is the leading cause of mortality globally. The high mortality rate is attributed to the lack of any signs and symptoms shown by the body and is hence known as a silent killer (1). The reported mortality rate is greater than 12.8 % covering 7.5 million people in the world. In the last decade, the mortality rate has doubled affecting the aged 18-70 years people. During the COVID-19 pandemic and post-pandemic a huge surge in cardiovascular diseases (CVD) was observed sharply. High blood pressure is not only in the heart but also in the prime organs of the body such as the brain, kidney liver, etc. The notable causes of CVD are mainly genetic, age-related, obesity, unhealthy diet and lifestyle, lack of physical exercise, kidney diseases, diabetic conditions, etc (2).

Azelnidipine (AZN) is a third-generation and long-acting calcium channel blocker (CCB) and recommended for the therapy of exciting rise in blood pressure and other cardiovascular complications. AZN is superior to 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 recent investigation is aim with enhancing the solubility, and dissolution rate and thereby hastening the absorption, bioavailability, and therapeutic efficacy of AZN by developing Liquisolid tablets that are administered orally. Furthermore, to estimate

the adsorption potential of mesoporous silica on the liquisolid blends of Azelnidipine (3),(4).

The greatest accuracy, stability, safety, and economy, along with higher patient comfort and compliance achieved through oral drug delivery (5). However, these benefits work only when the active ingredient is soluble in the gastrointestinal tract. One of the major hurdles in oral drug delivery as well as in the pharmaceutical industry is the poor solubility of the active pharmaceutical ingredient. The high-thoughtful screening processes in the designing of new chemical entities enabled them lipophilic in nature which is the prime requisite for crossing through the GI barrier (6) (7).

The hydrophobic molecule is converted into liquid medicament by utilizing a non-volatile solvent (NVS). This process of altering solid into liquid and transforming liquid into free-flowing compressible powder is known as the Liquisolid Compact technique (LCT) (8). The conversion of liquid into solid chiefly be governed by the adsorption potential of the carrier and coating agent. The Liquisolid Compact technique is a highly economical, easily scalable technique primarily utilized for active ingredients with a therapeutic dose of 1-100 mg. Those molecules having high therapeutic doses create high-weight tablets which is a problem for the person with dysphagia and children (9). Currently, mesoporous silica (MPS) has gained tremendous attraction for improving the solubility and dissolution rate of hydrophobic active ingredients and thereby enhancing oral bioavailability. Moreover, MPS also protects the active ingredient from degradation due to oxidation, hydrolysis, elevated temperature, and humidity, hence providing excellent stability. According to the FDA, MPS is biocompatible and safe to administer, hence widely incorporated in convention and nanotechnology-based approaches (10). These particles existed in micron size and possess hollow cavities for encapsulation of active ingredients. Additionally, the potential of adsorption on the surface of active molecules. Thus, several BCS-II molecules' solubility was improved and utilized for controlled or targeted delivery (11) (12). The MPS offers several benefits such as controllable pore size, microparticles, greater stability, higher specific surface area, surface modification, larger pore volume, low density, and maximum loading potential for active ingredients (13),(14).

The implementation of QbD enable the product with quality, safety and efficacy. The critical quality attributes are relying on the disintegration (DT) and dissolution. The designing of LCT is based on the incorporation of carrier agent (MCC 102), adsorbent (mesoporous silica) and superdisintegrant (Cross Povidone (CP)). The carrier agent (MCC 102) was essential for good compaction characteristics. The maximum adsorption efficiency of coating agent/adsorbent (mesoporous silica) determines the final weight of the tablets. Greater the adsorption potential then lesser is the total weight of tablets. LCT is a immediate release tablets, hence Cross Povidone worked as superdisintegrant for the prompt release.

Materials and Methods

Azelnidipine was received from Ajanta Pharma, Aurangabad. Parteck SLC 500 was received as a gift sample from Merck Pharmaceuticals, Mumbai. MCC 102 and sodium stearyl fumarate were delivered by Nitika Pharmaceuticals, Nagpur. Cross Povidone was delivered by Ashland Pharma, Mumbai.

Evaluation of Melting point and Loss on drying (LOD) of AZN

The original identity of the active ingredient was tested by estimating the melting point of the compound by digital melting point apparatus. The percentage of loss on drying (LOD) by estimated by placing accurately weighed 1g of AZN powder in hot air oven at 105 ^{o} C for about 2 h (16).

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Scrutiny of NVS

The first step in the Liquisolid Compact technique is the scrutiny of the best suitable NVS specifying the highest solubility for AZN. The fixed quantity (8 mg) of powder sample of AZN was cautiously shifted into 5ml of test tubes encompassing several NVS such as Tween 20, Tween 80, Span 80, Polyethylene glycol 200 and 400 grades, propylene glycol, etc. Moreover, all these test tubes were positioned on the vortex mixer so that the powder sample was allowed to mix properly. Lastly, the tasters were introverted and investigated by UV visible spectrophotometrically at 255 nm to assess the highest solubility of AZN (15).

Assessment of loading potential

The participation of non-volatile solvents in the progress of Liquisolid Compact produced wet mass. Hence, assessment of the adsorption potential of carrier and coating agent is essential for the build-up of Liquisolid compact tablets. The carrier agent MCC 102 and coating agent Parteck SLC 500 were liable for the free-flowing characteristics of the powder. The liquid burden aspect was premeditated from the succeeding equations (17).

$R = Q/ q$ ……1

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

$Q = W/L_f$ ……3

In the above equations, R represent the excipient proportions, extent of carrier agent with Q and coating material was q. Lf is the load factor and the flowing potential of the liquid (Φ) and its compressible potential (¥).

Fourier-Transform Infrared study (FTIR)

The greater therapeutic efficacy can be predicted when there will not be any interaction of active ingredients with their components. Hence, the interaction studies are of great significance. The compatibility studies were investigated with FTIR (IRAffinity-1s, Shimadzu). The AZN powder was blended with MCC 102 , and Parteck SLC and further scanned between the ranges of 400 to 4000 cm^{-1}. (18)

Optimization

The optimization of the LC was carried out by seeing 3-independent and 2-dependent factors. The formulation ingredients such as MCC 102 (X1), Parteck SLC (X2), and Cross Povidone (X3) were selected as independent parameters. From the perspective of tablets, disintegration time (Y1) and in-vitro dissolution release (Y2) which determine the patient's therapeutic efficacy, hence considered as dependent parameters. For the execution of QbD, the Design of Experiment (DoE, Statease, and Version 13) was utilized and the Box-Behnken design was best suited for the optimization which predicted 12 runs (19the impacts of two independent factors, i.e., excipient ratio (carrier:coating) (20).

Investigation of powder flowing characteristics

The powder blends which comprised of weight of 30 tablets were assessed for bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio for 12 randomized batches. The bulk density apparatus was utilized for the determination of bulk densities which measures the bulk mass and volume. Similarly, tapped densities of all powder blends were determined by tapping the cylinder about 100 times and recorded the volume. The angle of repose was assessed with the fixed funnel method. The Hausner's ratio is the proportion of tapped density/bulk density.

Formulation of Liquisolid tablets of AZN

The designing and development of the Liquisolid compact technique is based on calculating the minimum amount of carrier and coating agent for the final weight of the tablets. Before, the finalization of the weight of tablets minimum variable quantities in their higher to lower amounts were added and assessed for flowing behavior.

The precise extent of the AZN was transferred in the mortar succeeding NVS. The predetermined quantities of MCC 102 and Parteck SLC were incorporated to create the powder in their compressible nature. Moreover,

Cross Povidone (CP), and sodium steraryl fumarate (SSF) were added and blended without any friction. The powder mass was subjected to compression and tablets were prepared with a 10 mm punch size on 12 station multi-tooling machine (21). The components are represented in Table 1.

Table 1: Formulation of Liquisolid Compact Tablets of AZN

Batch	AZN	PEG 400	MCC 102	SLC 500	CP	MS	TALC	TOTAL
	mg	mg	mg	mg	mg	mg	mg	
F1	8	13	235	60	17.5	3.5	3.5	340
F2	8	13	250	50	10.5	3.5	3.5	338
F3	8	13	250	60	14	3.5	3.5	352
F4	8	13	220	60	14	3.5	3.5	322
F5	8	13	220	50	17.5	3.5	3.5	315
F6	8	13	250	50	17.5	3.5	3.5	345
F7	8	13	250	40	14	3.5	3.5	332
F8	8	13	220	40	14	3.5	3.5	302
F9	8	13	235	40	10.5	3.5	3.5	313
F10	8	13	235	60	10.5	3.5	3.5	333
F11	8	13	220	50	10.5	3.5	3.5	309
F12	8	13	235	40	17.5	3.5	3.5	321

Table 2 Box-Behnken model for the LCT of AZN

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:MCC 101	B:Parteck SLC	C:CP	DT	Dissolution
		mg	mg	mg	min	%
7	1	235	60	17.5	4.1	99.08
10	2	250	50	10.5	4.25	98.3
1	3	250	60	14	4.2	98.47
3	4	220	60	14	4.17	98.6
11	5	220	50	17.5	4.05	99.31
9	6	250	50	17.5	4.11	98.95
12	7	250	40	14	4.18	98.39
4	8	220	40	14	4.15	99
5	9	235	40	10.5	4.21	98.27
8	10	235	60	10.5	4.23	98.14
2	11	220	50	10.5	4.16	98.34
6	12	235	40	17.5	4.08	99.11

Estimation of Liquisolid Compact Tablets

Weight variation test

The 20 tablets were unsystematically hand-picked and precisely weighed. The mean weight of individual tablets was distinguished with standard derivations. The weight variation test permits within 2.5 % variations from the average tablets as per the specifications of Indian Pharmacopoeia (I.P) 2022 (18).

Crushing strength

It was confirmed by a Monsanto hardness tester by picking 3 tablets randomly from each batches.

Friability

The tablets weighed corresponding to 6.5 g retained in the Roche friabilator at a velocity of 25 rpm for 100 spins. After alternation, tablets were poised and reweighed. The percentage of the friabilator was premeditated by subtracting the weight of the preliminary from the concluding weight (22). According to the I.P. the acceptable limit is less than 1 %.

Disintegration time

The 6 tablets were casually hand-picked and positioned in the apparatus inclosing 900 ml of simulated gastric fluid (pH 1.2 HCl buffer) at 37±0.5° C. The time essential to screen the entire particles from sieve number 10 was noted.

Dissolution studies

The USP Dissolution apparatus II (Paddle) using pH 1.2 HCl buffer was implemented. The paddle was permitted to switch at a speed of 50 rpm, at 37±0.5° C. The models were introverted at 5 minutes, diluted, filtered through a 0.41 µm membrane filter, and scrutinized spectrophotometrically at 241 nm 23. The procedure was carried out in triplicates.

Assay

The 10 tablets were arbitrarily nominated and transformed into the powder. The mean weight of the tablet comprising a powder was dissolved with pH 1.2 HCl buffer. The solution was further diluted and filtered through a 0.45 µ membrane filter and scrutinized spectrophotometrically at 241 nm (24)

Stability study

The improved batch was tested according to the ICH guidelines at 40^0 C and 75 % RH for 90 days. The trials were quiet at 30 days and assessed for drug content, disintegration, and dissolution time (25).

Results and Discussion

Preformulation studies

The powder sample was investigated carefully for its organoleptic characteristics and observed yellow color powder with crystalline nature. The sample of 1 g was placed in the digital hot air oven at a temperature of 105 ^{0}C for about 2 hr. and identified 0.37 % loss of material. The solid powder sample was melted in the range of 193-195^0 C. The basic intention of performing the organoleptic estimation was the identification of azelnidipine. The outcome indicated the originality of the pure drug.

Scrutiny of NVS

The NVS served as a solubilizer for upgrading of solubility and dissolution rate of hydrophobic molecules. The solubility of AZN was estimated among the numerous non-volatile solvents and noted best in the PEG 400 (59 mg/ml) than PEG 200 (51 mg/ml), Span 80 (29 mg/ml), Tween 80 (24 mg/ml), Propylene glycol (19 mg/ml), Tween 80 (14 mg/ml). Hence, PEG 400 was chosen for the improvement of the solubility of AZN for higher solubilization and clarity in the solution.

Fourier-Transform Infrared study (FTIR)

The physical interactions among the AZN and excipients were checked with FTIR. Preceding that, the uniqueness of AZN was judged by scanning at a series of 400-4000 cm^{-1} and confirmed the originality. The FTIR spectra of the pure sample of AZN were shown in Fig. 1. The peaks obtained from Fig.1. were 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 existence of these functional groups confirmed the distinctiveness of AZN. The efficacious formulation should not have any interaction with their components, which impacts the therapeutic efficacy. The spectrum and bands of AZN were not shifted even after the combination of MCC, Parteck SLC and cross povidone. Hence, it was interpreted that AZN does not have any physical and chemical interactions with its formulation ingredients. The interaction studies with excipients were represented in Fig.2 to 4 respectively.

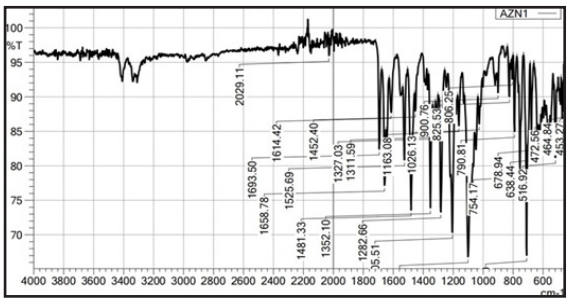


Fig. 1: The FTIR spectrum of AZN

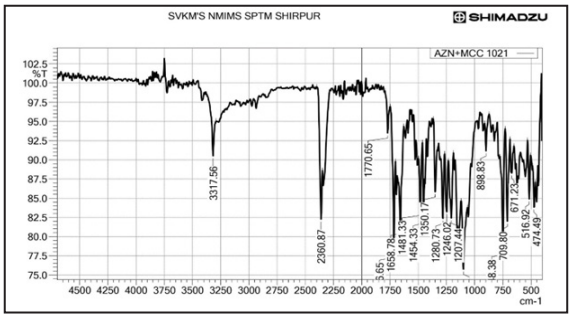


Fig. 2: The FTIR spectrum of AZN and MCC 102

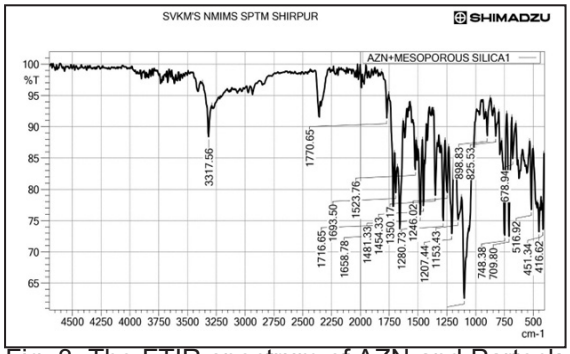


Fig. 3: The FTIR spectrum of AZN and Parteck SLC

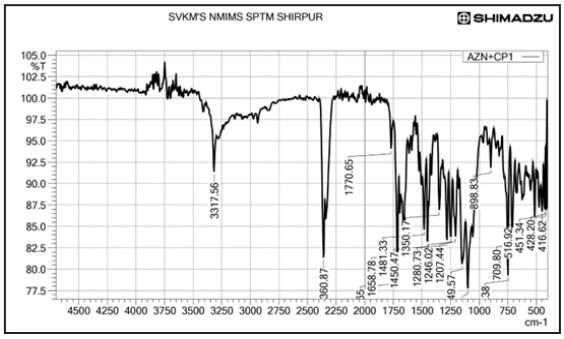


Fig. 4: The FTIR spectrum of AZN and Cross povidone

Optimization

The QbD was employed for the systematic development of formulations with minimum trials and maximum therapeutic efficacy. The concentration of carrier agent MCC102, coating agent Parteck SLC and superdisintegrant Cross Povidone (CP) opted as independent factors. The therapeutic efficacy of the tablet's dosage forms is proven by their disintegration time and percentage of drug release. Hence, these are the critical quality attributes (CQA) for the development of Liquisolid Compact tablets. According to these factors, the Box-Behnken design (BBD) was selected for providing the 12 possible randomized runs represented in Table 3.

The outcomes of the disintegration test and in-vitro drug release were applied to the ANOVA which suggested a quadratic model. The models for both these dependable factors were found significant with their p-value less than 0.05. The p-values for disintegration and for dissolution were 0.0238 and 0.0082 respectively. The ANOVA for their dependable parameters was depicted in Tables 3 and 4 respectively.

The BBD displayed the polynomial quadratic equations illustrated below in equations 1 and 2 for disintegration time and dissolution respectively. The impact created by all independent parameters (MCC 102, Parteck SLC, and CP) was showed by the terms A, B, and C in Equation 1. The plus and minus signs in

Table 3: The ANOVA model for the DT

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0412	8	0.0052	15.07	0.0238	significant
A-MCC 101	0.0057	1	0.0057	16.63	0.0266	
B-Parteck SLC	0.0008	1	0.0008	2.32	0.2253	
C-CP	0.0325	1	0.0325	95.16	0.0023	
AB	0.0000	1	0.0000	0.0000	1.0000	
AC	0.0002	1	0.0002	0.6585	0.4765	
BC	0.0000	1	0.0000	0.0000	1.0000	
A^2	0.0008	1	0.0008	2.34	0.2235	
B^2	0.0021	1	0.0021	6.18	0.0888	
C^2	0.0000	0				
Residual	0.0010	3	0.0003			
Cor Total	0.0422	11				

Table 4: The ANOVA model for the dissolution

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.75	8	0.2184	31.42	0.0082	significant
A-MCC 101	0.1482	1	0.1482	21.32	0.0191	
B-Parteck SLC	0.0302	1	0.0302	4.35	0.1283	
C-CP	1.45	1	1.45	207.91	0.0007	
AB	0.0576	1	0.0576	8.29	0.0636	
AC	0.0256	1	0.0256	3.68	0.1508	
BC	0.0025	1	0.0025	0.3597	0.5909	
A^2	0.0024	1	0.0024	0.3525	0.5945	
B^2	0.0242	1	0.0242	3.48	0.1589	
C^2	0.0000	0				
Residual	0.0208	3	0.0069			
Cor Total	1.77	11				

the below equation represented the synergistic and antagonistic effects respectively. In equation 1, the synergistic effects were predicted by the concentration of carrier and coating agent whereas CP showed the antagonistic effects. Moreover, this equation also illustrates the effect on the disintegration time by the combined parameters and the square parameters.

$$DT = +4.13 +0.0268\ A +0.0100\ B -0.0592\ C +0.0000\ AB -0.0070\ AC +0.0000\ BC +0.0200\ A^2 +0.0325\ B^2 +0.0000\ C^2 \quad \text{Equation 1}$$

$$\text{Dissolution} = +98.73 -0.1368\ A -0.0618 +0.3946\ C +0.1200\ AB -0.0743\ AC +0.0232\ BC -0.0350\ A^2 -0.1100\ B^2 +0.0000\ C^2 \quad \text{Equation 2}$$

In equation 2, the synergistic effects were suggested by the concentration of cross povidone and the antagonistic effects by the concentration of the carrier and coating agents. Moreover, when the carrier agent combines with the coating agent as well as the coating agent with superdisintegrant then synergistic effects were observed by the polynomial quadratic equation showed in equation 2. The effects of all independent factors on the dependent factors were shown with the help of 2-D Contour plots and 3-D response surface plots respectively in the Fig. 5 to 8 .

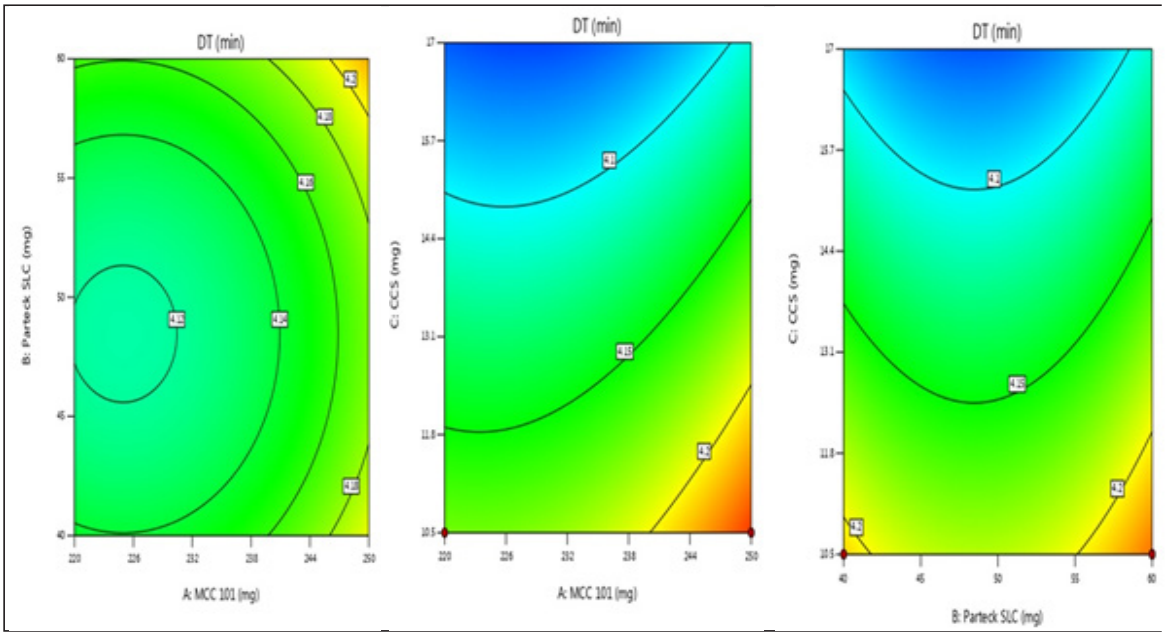


Fig. 5: 2-D Contour plots for the disintegration time

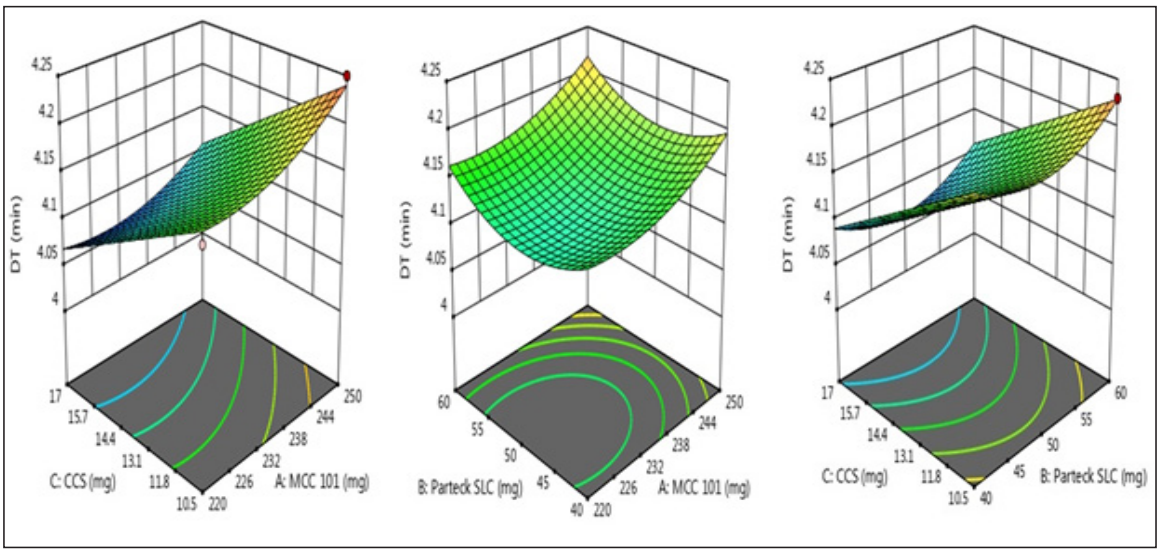


Fig. 6: 3-D surface response plots for the disintegration time

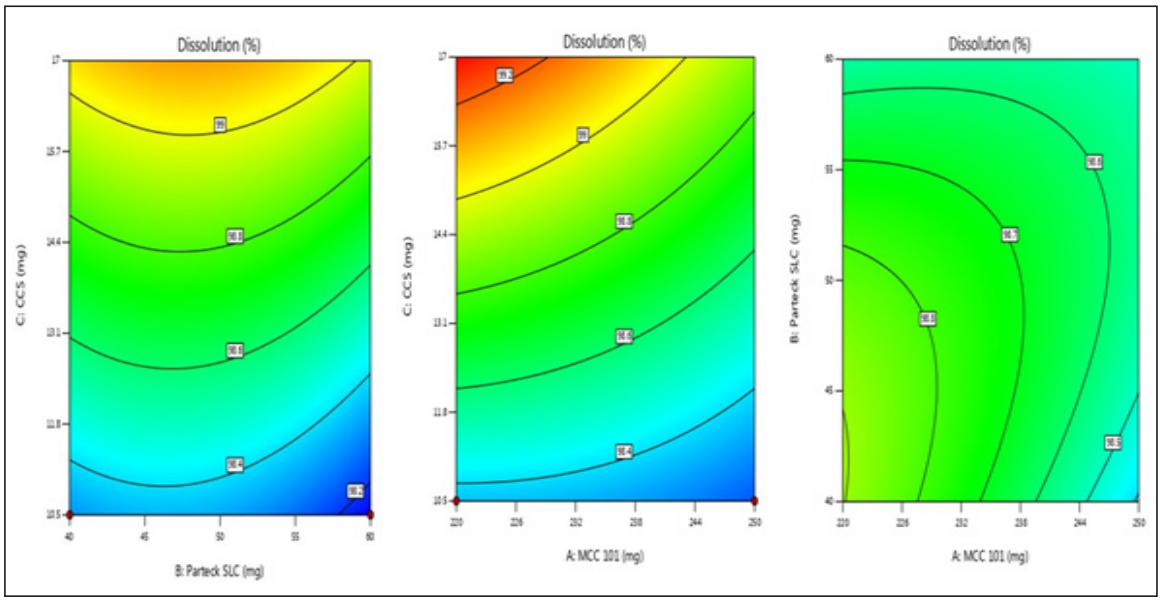


Fig. 7: 2-D Contour plots for the dissolution

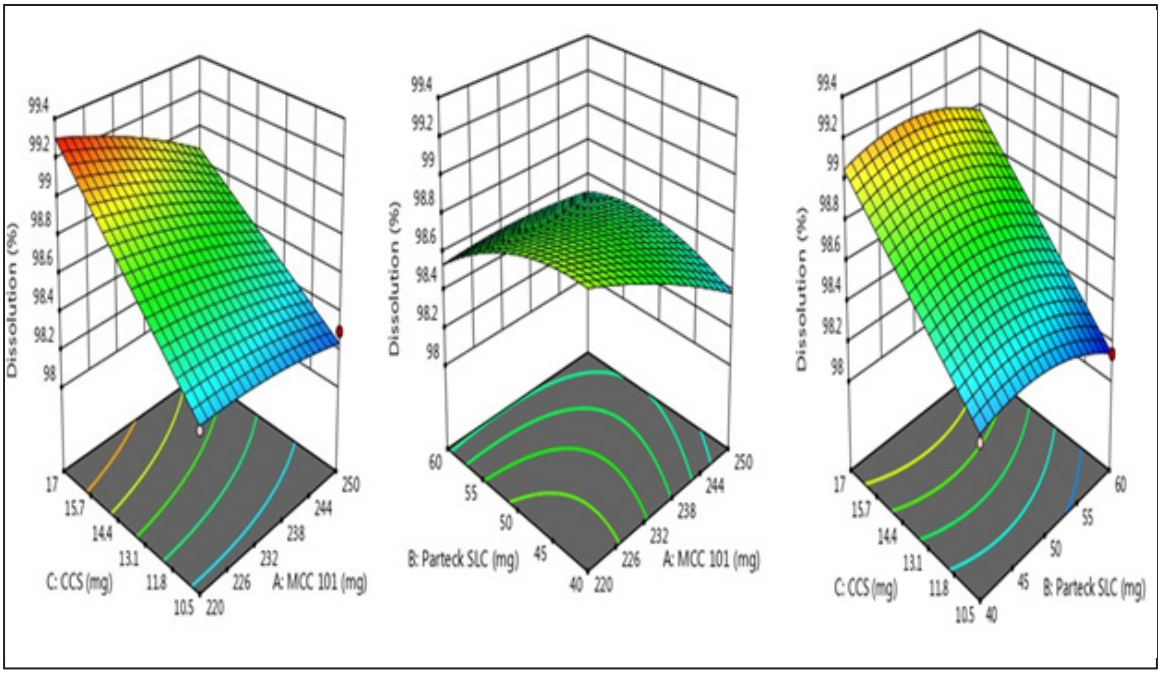


Fig. 8: 3-D surface response plots for the dissolution

Investigation of powder flowing characteristics

The flowing characteristics of powder blends were assessed for their as bulk density, tapped density, Carr's index, angle of repose, and Hausner's ratio. The powder blends of all batches reflected good flow properties which were calculated by Carr's index and angle of re-

pose values. The Parteck SLC possesses extreme surface area and liquid adsorption potential which creates free-flowing powder blends. The bulk densities were recorded in the range of 0.42±0.08 to 0.45±0.07, tapped density range between 0.49±0.08 to 0.53±0.07, Carr's index values between 10.20±0.44 to 19.23±0.33, angle of repose 20.74±0.38 to 29.93±0.40 and Hausner's ratio in the range of 1.11±0.09 to 1.23±0.18. The flowing characteristics results are depicted in Table 5.

Table 5: Flowing characteristics of powder blends

Batch	BD	TD	CI	Angle of repose	HR
F1	0.45±0.07	0.51±0.012	11.76±0.46	22.78±0.50	1.13±0.08
F2	0.43±0.09	0.49±0.14	12.24±0.39	23.56±0.44	1.13±0.05
F3	0.44±0.11	0.49±0.08	10.20±0.44	20.74±0.38	1.11±0.09
F4	0.42±0.08	0.5±0.10	16±0.53	26.46±0.48	1.19±0.10
F5	0.43±0.04	0.51±0.13	15.68±0.40	26.17±0.52	1.18±0.12
F6	0.44±0.08	0.49±0.09	10.20±0.49	20.83±0.46	1.11±0.09
F7	0.44±0.12	0.5±0.06	12±0.36	23.27±0.36	1.13±0.06
F8	0.42±0.06	0.52±0.10	19.23±0.32	28.62±0.41	1.23±0.14
F9	0.42±0.11	0.5±0.12	16±0.37	29.93±0.40	1.19±0.16
F10	0.43±0.10	0.5±0.14	14±0.28	24.77±0.51	1.16±-.12
F11	0.42±0.08	0.51±0.08	17.64±0.33	27.68±0.47	1.21±0.18
F12	0.44±0.07	0.53±0.07	16.98±0.35	28.23±0.44	1.20±0.14

All values n= 3 ±SD

Assessment of LC Tablets

The Liquisolid Compact tablets were exposed for weight variation, hardness, friability, disintegration, and content uniformity. The formulated batches approved the weight variation test according to the limits prescribed for 300-350 mg of tablets according to the Indian Pharmacopoeia. The hardness was confirmed with the Monsanto hardness tester and initiated at 4.6±0.06 to 5.0±0.09 kg/cm^2. The minor differences in the hardness for dissimilar batches were credited to the unlikeness of the amount of materials. The friability was estimated using the Roche friabilator and observed in the range of 0.37±0.19 to 0.42±0.30 %. According to the Indian Pharmacopial standard, the limit prescribe was less than 1 %, hence all the batches qualify for the friability test.

Similarly, the friability of tablets relies on the hardness, hence slight variance was detected during the assessment of friability. Tablets of all the batches were disintegrated at a time of 4.05±0.08 to 4.25±0.20 min. The modifications in the disintegration were observed due to the variable concentration of superdisintegrant. Tablets comprised of greater concentration have a rapid swelling tendency and thus the liberated quickly. The content uniformity of all batches was perceived in the series of 98.64±0.60 to 99.28±0.48 %. The results are illustrated in Table 6.

Table 6: The evaluation of Liquisolid Compact tablets

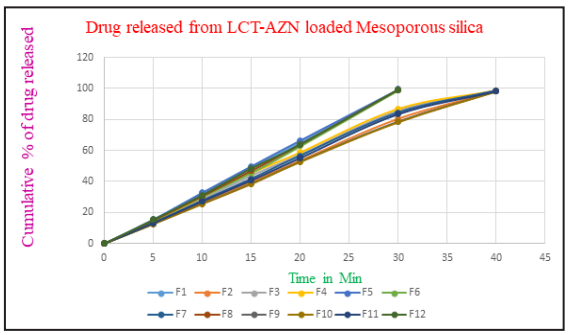
Batch	Weight variation	Hardness	Friability	Disintegration	Content uniformity
F1	340±0.65	4.6±0.06	0.41±0.21	4.10±0.13	99.28±0.48
F2	338±0.74	4.8±0.03	0.38±0.27	4.25±0.20	98.89±0.84
F3	352±0.85	5.0±0.05	0.37±0.19	4.20±0.16	98.71±0.67
F4	322±0.61	4.8±0.06	0.39±0.12	4.17±0.12	99.12±0.71
F5	315±0.59	4.6±0.07	0.42±0.30	4.05±0.08	99.23±0.58
F6	345±0.70	4.7±0.08	0.40±0.25	4.11±0.14	98.90±0.74
F7	332±0.66	4.6±0.10	0.42±0.19	4.18±0.09	98.64±0.60
F8	302±0.82	4.7±0.07	0.40±0.10	4.15±0.05	98.83±0.73
F9	313±0.74	5.0±0.09	0.38±0.17	4.21±0.10	98.94±0.67
F10	322±0.54	4.9±0.11	0.38±0.24	4.23±0.20	98.79±0.95
F11	309±0.82	4.7±0.08	0.40±0.26	4.16±0.15	98.84±0.56
F12	321±0.50	4.6±0.10	0.42±0.16	4.08±0.14	99.15±0.62

In-vitro dissolution release studies

The drug-released profile from the LCT tablets was achieved with an in-vitro type II dissolution apparatus. The LCT was entirely discharged within 30-40 min indicating an instant release profile and hence, the dissolution process was rapid. This prompt release of active ingredients was attributed to the transformation of solid drugs into liquid medicament. When this liquid medicament comes in contact with the dissolution media, ultimately process of dissolution gets faster than the conventional tablets. The marketed tablet comprised of 8 mg of AZN was released entirely after 70 min (93.78 %). Hence, the LCT is much better for the improvement of solubility and dissolution rate. İn marketed tablet formulation, drug remain in solid form and required a specific period for the dissolution.

Among the several batches tested, the highest amount of drug release was noted with F5, F1, F8 and F12 indicating 99.31 %, 99.08%, 99 % and 99.11 % within 30 min. Furthermore, F2, F3, F4 and F6 batch was completely released in 40 min with 98.30 %, 98.47 %, 98.60 % and 98.95 % respectively. The burst release of the active ingredient was due to the existence of a greater concentration of superdisintegrant in the formulation.

The drug released from F7, F9 to F11 was found to be 98.39%, 98.27%, 98.14 %, and 98.34% respectively within 40 min. The difference in all batches was similar to the changing concentration of composition and greater hardness was accountable for the slightly slower released of the medicament from the tablets. The drug release profile is shown in Fig. 9.



All values are n= ±3

Fig. 9: In-vitro drug released of AZN from Liquisolid Tablets (F1 to F12)

Stability studies

The optimized batch F5 was verified according to the ICH stability guidelines under 40 ^{0} C at 75 % relative humidity maintained in the stability chamber (Remi, Mumbai, India). The outcomes are described in Table 7.

Table 7: Stability assessment of an improved batch F5

Factors	Initial	30 Days	60 Days	90 Days
Hardness	4.6±0.07	4.5±0.10	4.3±0.06	4.2±0.11
Friability	0.42±0.30	0.44±0.20	0.46±0.16	0.48±0.30
Disintegration	4.05±0.08	4.03±0.04	3.59±0.10	3.55±0.12
Content uniformity	99.23±0.58	99.11±0.46	98.93±0.52	98.73±0.62

Conclusion

Azelnidipine is extensively suggested for the therapy of hypertension. The poor solubility and bioavailability restricted the therapeutic efficacy of the AZN. 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 F5 was chosen based on flowing characteristics, lowest disintegration time, and greater dissolution release within 30 min. Moreover, comparatively with remaining batches, the best results are obtained with the minimum quantity of the material which saves money. It was concluded that Parteck SLC possesses extreme surface area and good flowing characteristics and is easily compressible in nature with an enormous capacity for adsorption of the liquid medicaments. Hence, it is one of the best suitable carriers and coating agents utilized during the LCT. The LCT is a highly economical and rapid method compared with other solubility enhancement techniques. Hence, it was concluded that the Liquisolid Compaq technique is beneficial for refining the solubility and dissolution of lipophilic moieties.

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