RESEARCH PAPER

Integrated Solubility Enhancement and Tablet Formulation of Lercanidipine Hydrochloride Using Design of Experiments

Sanyasi Swain[1], Anjan Kumar Mahapatra[2]*, Asish Sahu[3] and Rajeshree Panigrahi[4]

[1]Formulation Research and Development, Hetero Labs Ltd. Hyderabad, Telangana, 500082
[2,3,4] Department of Pharmaceutics, Royal College of Pharmacy and Health Sciences, Andhapasara Road, Berhampur-2
*[1]royalsanyasi25@gmail.com, [2]*anjanmahapatra@gmail.com, [3]asishsahu24@gmail.com and [4]ranuroyal@gmail.com*

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ABSTRACT

Background: Lercanidipine hydrochloride (HCl) is a poorly soluble calcium channel blocker limiting its oral bioavailability and therapeutic efficacy. Increasing its dissolution rate through appropriate formulation methods is essential for improved clinical outcomes.

Methodology: Solid dispersions of lercanidipine HCl were developed using hydrophilic carriers poloxamer 188, polyethylene glycol 6000, and polyvinylpyrrolidone K30 by solvent evaporation and fusion techniques at different drug-to-carrier ratios. Dispersible tablets were formulated from these solid dispersions, and optimization was performed using a 23 factorial design under Quality by Design principles. Characterization was conducted using FTIR, DSC, XRD, and dissolution studies, along with evaluation of tablet physical parameters such as content uniformity, hardness, friability, and disintegration time.

Results: Solid state analyses confirmed successful drug incorporation into carriers without significant interaction or loss of stability. Among formulations, poloxamer 188 (1:1 ratio) yielded the highest drug dissolution rate. The optimized tablet exhibited 99.98 % drug release within 45 min, fast disintegration (1-2 min), and satisfactory mechanical strength. Statistical analysis (ANOVA, p = 0.0113) indicated sodium starch glycolate and sodium lauryl sulfate as key variables influencing outcomes.

Conclusions: Solid dispersion strategies and factorial design optimization markedly improved the dissolution and disintegration properties of lercanidipine HCl tablets. These findings suggest practical approaches for formulation of fast-dissolving oral lercanidipine preparations that can enhance patient benefit and pharmaceutical quality.

Keywords: Solid dispersion; solubility; PEG 6000; poloxamer 188; polyvinyl pyrolidone (PVP K30); lercanidipine HCl; Design of Experiment.

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INTRODUCTION

The rationale for product development lies in improving dissolution rates of poorly soluble drugs (BCS Class II). Although these drugs do not face permeability issues, their in vitro release can be enhanced by increasing solubility. A feasible method of increasing the solubility is obtaining the solid dispersions (SDs) of low soluble drug in an inert hydrophilic carrier [1].

The solid dispersion technique reduces particle size of the active ingredient to a molecular level, thereby improving wettability and dissolution. It is a widely used, cost-effective strategy for enhancing drug release [2, 3].

To enhance the solubility of a low soluble drug, different carriers of hydrophilic nature is utilized. Many works have been carried out with different hydrophilic carriers like, Transcutol HP, Poloxamer 188, Poloxamer 407, Eudragit E100, polyethylene glycol (4000, 6000, 8000 etc.), Gelucire 44/14, Solutol® HS15, for enhancement of solubility of low soluble drugs [4, 5].

Lercanidipine HCl (LER) is categorised to BCS Class II drugs, has very low solubility which leads to poor drug release and low bioavailability. The work is aimed to enhance the solubility of lercanidipine HCl by different methods and using various carriers. The identification and solid state characterisation of the dispersions can be carried out by differential scanning calorimetry (DSC). Infra-red spectroscopy analysis is used to identify drug-carrier interaction study, and for crystalline structure identification X-ray diffraction technique was used. Finally, a stable tablet formulation was prepared by using the selected and compatible excipients [6 -9].

MATERIALS AND METHODS

Materials

*Author for Correspondence: anjanmahapatra@gmail.com

Lercanidipine HCl (LER), poloxamer 188, PEG 6000, SLS and microcrystalline cellulose were received from Aurobindo Pharma Limited, Hyderabad, India as a gift samples. Povidone K30 was received from Balaji Amines Limited, Hyderabad, India. Sodium starch glycolate, magnesium stearate, talc were received from research lab Pellets Pharma Limited, Hyderabad, India as gift sample. Analytical grade chemicals and solvents were used for all the research purpose.

Experimental work

Preparation of SDs

The drug and the carrier(s) like, poloxamer 188, PEG 6000 and PVP K30were used in obtaining the solid dispersions by using solvent evaporation and melt or fusion techniques at w/w ratios of 1:1, 1:2 and 1:3.

Solvent evaporation technique

Ethanol was taken and to that required amount of carrier and LER was dissolved. Then the mixture was placed under sonication for 30 min. The solvent was removed under vacuum by help of a rotary flask evaporator at 40 ºC until the solid dispersion was dried. Collected the dried mass and scraped, sifted the materials by using # 30 mesh sieve and stored in a desiccator.

Melt or Fusion Technique

The carrier was melted at 60°C and added the measured amount of LER under stirring. Then the melted carrier and drug dispersion was suddenly cooled by using an ice bath. The SDs prepared was scrapped and sifted by pouring through 30 mesh sieve and stored in a desiccator for further use [10].

Evaluation of SDs

***In vitro* dissolution studies**

The dissolution study of SDs was performed by using the dissolution media 0.1N HCl of 900 mL using USP paddle (ELECTROLAB, Mumbai, India) at 37 ± 0.5 °C. After each time interval 5 mL of sample was withdrawn and same was volume replaced with fresh media. Then[6] the samples were analysed spectrophotometrically at 236 nm to analyze the quantity of drug released [11-14].

Solid state characterization of SDs

Solid-state studies were performed for lercanidipine HCl, poloxamer 188, PEG 6000, PVP K30 and the prepared solid dispersions.

Infrared spectroscopy (FTIR)

FTIR spectrophotometer (Alpha, Bruker, Germany) was used to perform IR analysis. The IR spectrum was reported in the range of 4000–600 cm^{-1}. Different spectrum outcomes for drug, carrier and the solid dispersions were compared [15].

Differential scanning calorimetry (DSC)

Thermal behaviour of samples were determined by using DSC-PYRIS-1. Dry nitrogen environment between -8 mW to 20 mW was maintained to perform the DCS scanning [16].

X-ray diffraction (XRD)

X' Pert Model, Phillips was used to perform the X-ray diffraction scatter of selected batches of solid dispersion by which the physical form of the drug molecule was to characterized [17].

Drug Content study

The equivalent weight of the DSs were added into 50 mL 0.1N HCl pH 1.2 and stirred continuously for 24 hours. The solution was filtered, suitability dilution and analysed at 236 nm using a UV spectrophotometer [18].

Formulation of dispersible tablets

The selected SDs, MCC PH102 SD, PVP K30, sodium starch glycolate (SSG) and talc were sifted by using ASTM (American standard of test and measurement) mesh no. #30 blended and lubricated for 5 mins with SLS. The blend was compressed to get the tablets. Rotary tablet compression machine (Cadmach's tablet press) used with 9 mm round standard concave punches. The factorial design $2^3$was used, where three variables A, B and C and two levels which is lower and higher concentration of functional excipients. Nine trial runs were prepared including central one (optimised) and evaluated for pre compression and post compression parameters. The experiment design details and formula of 2^3 factorial designs of lercanidipine HCl tablets are given in **Table 1**.

Table 1: Formula for dispersible tablet

Sr. No.	Ingredients / Mixing and blending step	mg/unit								
		FM1	FM2	FM3	FM4	FM5	FM6	FM7	FM8	FM9
1	Lercanidipine HCl SDs (equivalent to 20 mg of drug)	42.4	42.4	42.4	42.4	42.4	42.4	42.4	42.4	42.4
2	Microcrystalline cellulose (MCC PH102 SD)	146.6	144.6	142.6	145.6	150.6	146.6	144.6	148.6	140.6
3	PVP K30	8	12	12	10	8	12	8	8	12
4	Sodium starch glycolate (SSG)	8	4	8	6	4	4	8	4	8
5	Talc	2	2	2	2	2	2	2	2	2
	Sodium lauryl sulphate (SLS)	3	5	3	4	3	3	5	5	5
	Weight of tablet (mg)	**210**	**210**	**210**	**210**	**210**	**210**	**210**	**210**	**210**

Pre-compression parameters

Parameters like flow property, density of material, compressibility index, Hausner's ratio, were determined for all the batches.

Parameters of post-compression

Content uniformity test

As the drug content of the tablet is less than 25 % of tablet weight, according to USP content uniformity test is mandatory. Individual assay was performed by randomly selecting 20 tablets. For the assay of the tablets UV-spectrophotometer was used at 236 nm. As per the guideline the specification limit for the content uniformity should be from 85 % to 115 % and the acceptance value should be within 15 %.

Hardness

The hardness of the tablets was evaluated using 10 compressed tablets. Tablet crushing strength was determined with a Pharmatron (Sotax MT50 Multi-test Hardness Tester) tester. The hardness was maintained within the range of 60-100 N to ensure adequate mechanical strength.

Friability test

Roche friabilator (Electrolab) was used to perform the tablet friability test. As per US friability test if the tablet weight is less than or equal to 650 mg then 6.5 g of tablets to be taken for the test. Here 6.5 g of tablets were taken and marked as initial weight (W_0), then added to the rotating drum and allowed the drum to rotate at 25 rpm for 4 min (100 revolutions), and final weight (Wt) was measured. The percentage loss of table mass was calculated by using the, below formula. As per the guideline the % friability should not more than 1% w/w.

$$\text{Friability} = [(\text{Weight}_{\text{Initial}} - \text{Weight}_{\text{Final}}) / (\text{Weight}_{\text{Initial}})] \times 100.$$

***In vitro* disintegration test**

Tablet disintegration was performed by using USP disintegration test apparatus using 900 mL of purified water and the temperature was maintained at 37 ± 2 ℃. The disintegration time for the tablet should be not more than 15 min.

***In vitro* dissolution studies**

Dissolution studies were conducted using a USP type II (paddle) apparatus at 50 rpm in 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5 °C. Samples were withdrawn at predetermined intervals with replacement of fresh medium, and analyzed by UV–visible spectrophotometry at 236 nm. The study was conducted with six tablets (n=6), and the mean percentage cumulative drug release was calculated [19, 20, 21, 22, 23].

Factorial design

Factorial design was used to optimise the formulation by using DOE software and the responses were evaluated. Three factorial two level crossover design was used to optimise the formulation. The results represents that the change of the response due to the change of level of the factor from low to high and vice versa. The optimised formulation was selected by observing the response curve of the design.

Optimized formulation selection

DOE software version 11 was used optimise formula. On the basis of software response analysis the optimized formulation was selected.

RESULTS AND DISCUSSION

Solubility studies

The solubility of lercanidipine HCl in water is very poor i.e., 0.156 mg/L at 25 °C which is increased with the carrier that is 85 mg/mL at 37±0.5 ºC and the solubility increased with increase in the concentration of poloxamer 188, PEG 6000 and PVP K30.

Infrared spectroscopic studies (FTIR)

FTIR spectra of lercanidipine HCl were obtained using KBr pellets over 4000–600 cm^{-1} (Spectrum V5.3.1). The pure drug showed characteristic peaks for N–H (3202 cm^{-1}), aromatic C–H (3085 cm^{-1}), and C=O stretching (1681 cm^{-1}). Minor peak shifts observed in solid dispersions (e.g., C=O at 1695 cm^{-1}), suggesting improved dispersion without any major drug-excipient interaction. The FTIR peaks of lecarnidipine HCl with different carrier are illustrated in **Fig. 1.**

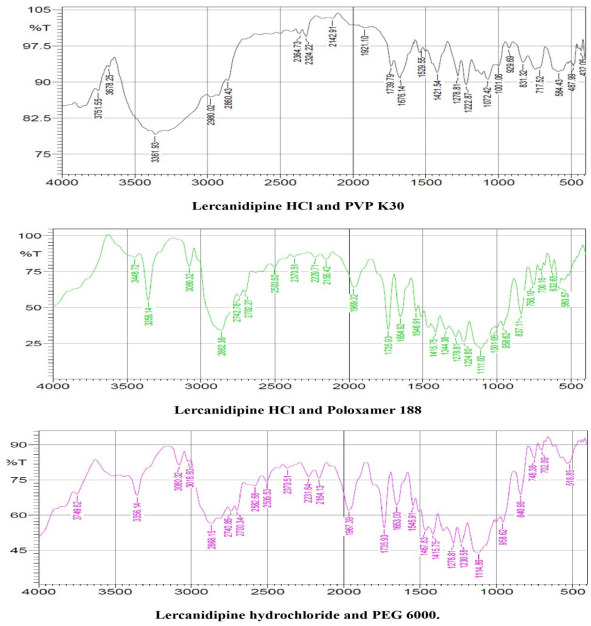

Fig. 1: IR Spectra of (A) Lercanidipine HCl and PVP K30 (B) Lercanidipine HCl with Poloxamer 188 (C) Lercanidipine HCl and PEG 6000

DSC

From the thermal studies it was observed that there is no changing in the melting point of the drug with an endothermic peak of LER observed at 178.5 ºC analogous to its melting point. While the endothermic peak corresponding to LER was absent at the same melting point which indicates that the drug was converted to amorphous form. The DSC thermogram is presented in **Fig. 2.**

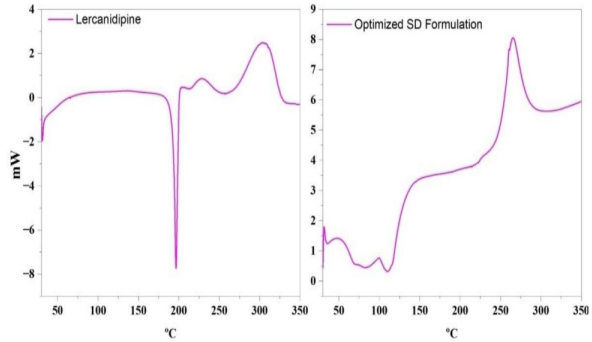

Fig. 2: DSC of pure drug and the optimised formulation (Lecarnidipine and poloxamer 188 1:1 w/w)

X-ray diffraction (XRD)

From the XRD diffraction pattern the drug molecule alone is a highly crystalline in nature which shows the sharp peak, whereas the formulation with the selected SDs having different diffraction pattern, that confirms the change in crystalline nature. The 2 θ value of pure LER is at 7, 18.9, 23.1 and 24.8 which is a crystalline form. The SDs prepared are not having the 2 θ values which indicates the crystalline form is converted to amorphous form. XRD interpretations were shown in **Fig. 3.**

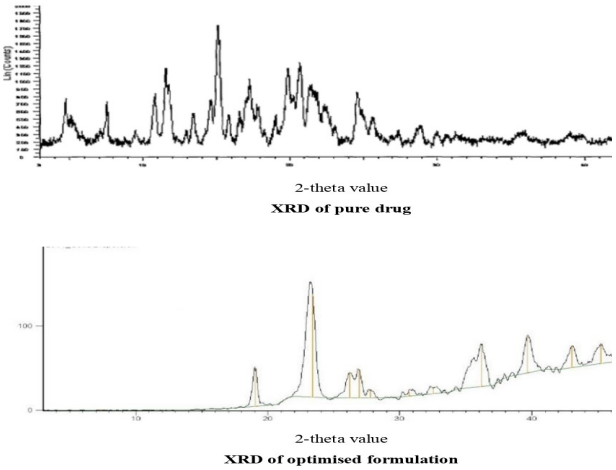

Fig. 3: XRD of pure drug and optimised formulation (Lecarnidipine and poloxamer 188 1:1 w/w)

Parameters of post compression

Tablets post compression parameters were mentioned in **Table 2**. The content uniformity or assays of all the nine formulations were within the limit and the percentage loss of mass (friability) also observed within the limit which shows sufficient crushing strength. The disintegration time observed 1 min for formula F4. Due to swelling nature of SSG tablets swell and disintegrate faster.

Table 2: Post compression Parameters

Std.	Run	Hardness(N)	% Drug Release	Disintegration Time (min)	CU (%)
2	1	65	88.15	4	99.15
5	2	70	85.54	2	99.43
4	3	66	91.61	3	99.67
3	4	70	99.98	1	99.73
1	5	68	80.85	3	99.32
8	6	71	80.77	4	99.34
6	7	75	94.95	2	99.57
7	8	68	82.93	4	99.74
9	9	69	96.95	3	100.05

In vitro drug release studies

The drug releases of all nine formulations (F1–F9) were mentioned in **Fig. 7**. The drug release rate of the formulation can be significantly increased by preparing the solid dispersion of drug and carrier. SDs with poloxamer188 shows higher drug release in tablet formulation. As the ratio of poloxamer 188 increase the drug release from the formulation also increased. A comparative dissolution profile of all formulations is shown in **Fig. 4** among which F4 is observed as the formulation showing highest drug release.

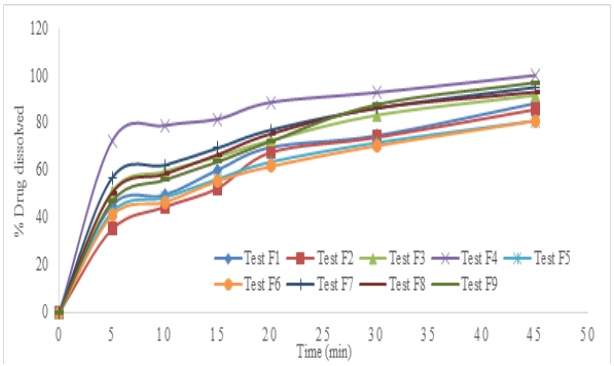

Fig. 4: Dissolution Profile of Different Formulations in 0.1N HCl, 900mL, Paddle at 50 rpm

Factorial Design and Optimization:

A 2^3 full factorial design was applied using Design-Expert® software (Version 11, Stat-Ease, USA) to evaluate the influence of three formulation variables: sodium starch glycolate (SSG, factor A), sodium lauryl sulfate (SLS, factor B), and PVP K30 (factor C). The responses measured were percentage drug release and disintegration time.

ANOVA analysis showed that the model was statistically significant ($p = 0.0113$, < 0.05), with SSG and SLS being major contributing factors. The model F-value (183.88) and adequate precision (43.65, > 4) indicated reliability of the model. The predicted and actual response values were in close agreement, confirming model validity.

The optimized formulation (F4) was identified at the central point of the factorial design. It demonstrated:

- **Drug release:** 99.98 % within 45 min
- **Disintegration time:** 1–2 min
- Acceptable hardness (60–100 N) and friability (< 1%)

Thus, F4 was finalized as the optimized formulation for dispersible tablets of lercanidipine HCl.

Table 3: 2^3 full factorial design with central point and response

Std.	Run	Fact 1 A:SSG	Fact 2 B:SLS	Fact 3 C:PVP K30	Resp 1 % Drug Release	Resp 2 Disintegration Time
2	1	8	3	8	88.15	3
7	2	4	5	12	85.54	4
6	3	8	3	12	91.61	2
9	4	6	4	10	99.98	1
1	5	4	3	8	80.85	5
5	6	4	3	12	80.77	4
4	7	8	5	8	94.95	2
3	8	4	5	8	82.93	4
8	9	8	5	12	96.95	2

Note: Run 4 is the central point in the 2^3 factorial designs which shows the significant response

Fit Statistics

Table 4: Fit statistics for the factorial design of the design experiment.

Std. Dev.	0.0003	**R^2**	0.9992
Mean	0.1062	**Adj. R^2**	0.9947
C.V. %	0.2586	**Pred. R^2**	NA[1]
		Adeq. Precision	43.6546

Adequate Precision evaluates the signal-to-noise ratio, where a value above 4 is considered acceptable. The obtained ratio of 43.655 demonstrates a strong signal, indicating that the model is suitable for exploring the design space.

Table 5: ANOVA for selected factorial model for the design experiment for % drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0001	6	0.0	183.88	0.0113	Significant
A-SSG	0.0001	1	0.0001	6.37		
B-SLS	0.0	1	0.0	213.70		
C-PVP K30	2.794E-06	1	2.794E-06	37.06		
AB	6.342E-07	1	6.342E-07	8.41		
AC	2.670E-07	1	2.670E-07	3.54		
ABC	9.180E-07	1	9.180E-07	12.18		
Curvature	0.0	1	0.0	567.64		
Residual	7.540E-08	1	7.540E-08			
Core Total	0.0001	8				

The model **F-value** of 183.88 indicates that there is only a 4.13% probability that such a high value could result from noise.

P-values less than 0.05 confirm the statistical significance of the model terms; in this study, factors A and B were significant, whereas terms with p-values above 0.1 were considered non-significant.

Half Normal Plot and Interaction

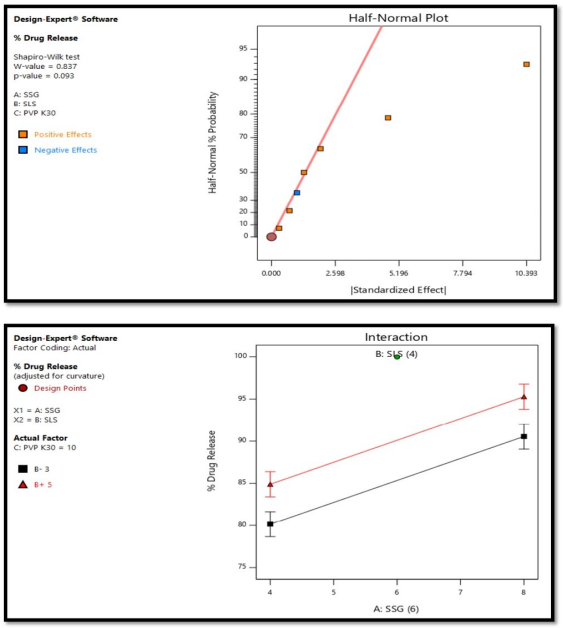

Fig. 5: Half normal plot and Combine interaction for the Design experiment

Observation: The half normal plot describes that there is no errors in the statistical F test and the probability of reaching the drug release is high. Interaction chart shows that there is no interaction of other factors in the design and also there is no interaction in between the factors. The half normal and combine interaction plots are presented in **Fig. 5.**

Predicted and Actual Values

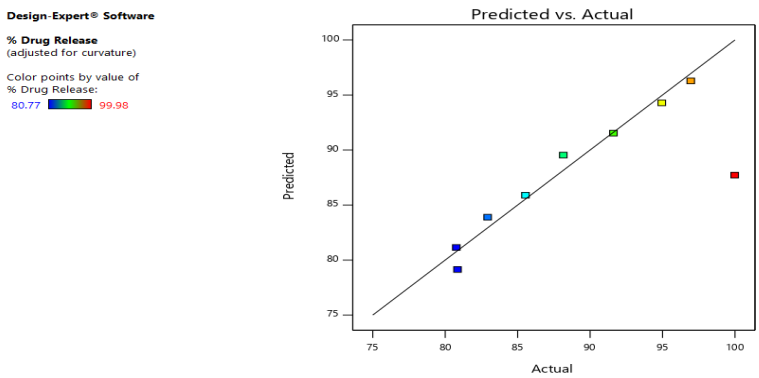

Fig. 6: Predicted and Actual Values drug release

Observation: From the plot it was observed and concluded that the predicted value and the actual value are similar and there is no significance difference.

REPORTS

Table 6: Detailed report on the outcomes for the design expert.

Run Order	Actual Value	Predicted Value[1]	Residual	Leverage	Internally Studentized Residuals	Externally Studentized Residuals	Cook's Distance	Influence on Fitted Value DFFITS	Standard order
1	0.1065	0.1066	-0.0001	0.875	-1.000	0.000	0.875	0.000	2
2	0.1081	0.1082	-0.0001	0.875	-1.000	0.000	0.875	0.000	7
3	0.1045	0.1044	0.0001	0.875	1.000	0.000	0.875	0.000	6
4	**0.1000**	**0.1000**	**0.0000**	**1.000[2]**					**9**
5	0.1112	0.1113	-0.0001	0.875	-1.000	0.000	0.875	0.000	1
6	0.1113	0.1112	0.0001	0.875	1.000	0.000	0.875	0.000	5
7	0.1026	0.1025	0.0001	0.875	1.000	0.000	0.875	0.000	4
8	0.1098	0.1097	0.0001	0.875	1.000	0.000	0.875	0.000	3
9	0.1016	0.1017	-0.0001	0.875	-1.000	0.000	0.875	0.000	8

[1] Predicted values at the center point include the center point coefficient.

[2] Cases with a leverage value of 1.0 show undefined residuals for studentized residuals, Cook's distance, and external study.

[3] Indicates values exceeding the specified limits.

***In vitro* disintegration time (DT)**

Disintegration time for tablet may be expressed by the response of the statistical design. From the design the P value that is0.0184represents the design is significant. Disintegration time of the compressed tablets observed in between 1 to 4 mins. From the design it was confirmed that the disintegration time of the tablets was slower with higher the value of PVP K30. This is due to the water uptake inside the tablet. Faster disintegration time can affect the drug release from the dosage form.

ANOVA for selected factorial model

Response 2: Disintegration Time

Table 7: ANOVA for selected factorial model of the design expert for disintegration time

Source	SoS	df	Mean Square	F-value	p-value	
Model	0.0000	0				
Curvature	4.01	1	4.01	3.17	0.0184	Significant
Residual	8.87	7	1.27			
Cor Total	12.89	8				

Where the P-values less than 0.05 indicate model terms are significant.

***In vitro* drug release**

Important study of the research was dissolution which can be expressed that the F value 6.37 indicates that the % drug dissolved is significant at the 6 mg of SSG. Also the P value of 0.0113results the design is significant ($P < 0.05$). The predicted R^2 0.9992 is reasonable agreement with the adjusted R^2 0.9947. This indicated the formulations are significant model terms. The percent release from the dosage form observed in between 82.93 to 99.98. Higher the drug release is due to the formation of SDs which is due to aqueous solubility. The research results that the SDs prepared with poloxamer 188 shows higher solubility and improves drug release.

Formulation optimization

Objective of optimization of a formulation was to find out the parameters affects to the formulation in different levels. The optimization also results the production of products with reproducibility and quality. The responses obtained from the design compared with the plots and the required out comes measured. From the design observed two responses that are disintegration time and % drug release which was used to clearly optimise the formulation. Run F4 which shows higher dissolution and with lower disintegration time which may be considered optimum formula for lercanidipine HCl tablets.

CONCLUSIONS

In vitro dissolution of lercanidipine HCl tablets may be increase by preparing the SDs with poloxamer 188, PEG 6000 and PVP K30. The SDs prepared with poloxamer 118 shows the higher solubility so the final tablet formulation prepared with SDs which prepared with poloxamer 188. To optimise the formulation DOE software (Stat Ease 11) was used where theresponse plots and contour plots were drawn with the use of by P Value and F value. The optimised formula F4 finalised with Design-Expert software (Stat Ease 11) that shows optimum hardness, disintegration time (1-2 min), and dissolution rate (99.98 %) in 45 mins is suitable for formulation of dispersible tablets. Lercanidipine HCl dissolution rate was increased by using the optimum quantity of SSG, PVP K30 and SLS in the formulation.

From the co-efficient of design of experiment, SSG, PVP K30 and SLS had prominent effect on percentage drug dissolved. The incorporation of optimised quantity of SSG, PVP K30 and SLS in lercanidipine HCl tablet shows synergistic effect on the drug release.

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CONFLICT OF INTEREST

The author(s) do not have any conflict of interest.

AUTHOR CONTRIBUTION

Sanyasi Swain contributed to writing the manuscript draft. Asish Sahu edited the manuscript. Anjan Kumar Mahapatra and Rajeshree Panigrahi reviewed, supervised and conceptualized the whole experimental work.

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