Available online on 15.02.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Design expert assisted mathematical optimization of solubility and study of fast disintegrating tablets of Lercanidipine Hydrochloride

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ABSTRACT

90% of drugs being researched today, posses poor solubility setback which inturn renders the drug with slower rate of absorption from the buccal route; hence dissolution is the rate limiting step for such lipophilic drugs. So, there is a need to keep a check on the dissolution profile of these drugs to ensure maximum therapeutic utilization. The dissolution rate therefore becomes a primary factor which governs the rate and extent of its absorption. Enormous work is being performed in the field of enhancement of solubility and dissolution behaviour of such drugs. Advancements and innovations have developed solid dispersion (SD) technique as the novel method for the solubility enhancement. Precision of dosing and patient's compliance is a crucial prerequisite for the management of chronic Antihypertensive treatment, So there arised a need to formulate a system which should resolve the difficulties associated with conventional tablets. This issue can be better tackled with the formulation of orally fast disintegrating tablets. The aim of the present study was to improve the solubility and dissolution rate of Lercanidipine hydrochloride (LRH) by formulating a solid dispersion with Polyvinyl pyrollidine (PVP-K30) and Guargum. Full Factorial designs are exploited to learn and research the effects of different variables on the quality determinant parameters. An appropriate statistical model was selected for the scrutiny of the enhanced dissolution pattern. Finally, these solid dispersions were incorporated into fast disintegrating tablets.

Keywords: Lercanidipine Hydrochloride, Solid dispersion, Statistical design approach, Melt fusion method, Fast disintegrating tablet, *In vivo* studies

Article Info: Received 30 Dec 2018; Review Completed 04 Feb 2019; Accepted 05 Feb 2019; Available online 15 Feb 2019

Cite this article as:

Saini S, Garg R, Design expert assisted mathematical optimization of solubility and study of fast disintegrating tablets of Lercanidipine Hydrochloride, Journal of Drug Delivery and Therapeutics. 2019; 9(1-s):172-180

DOI: http://dx.doi.org/10.22270/jddt.v9i1-s.2406

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INTRODUCTION

Due to the ongoing technological advancements in the pharma world of designing various drug delivery systems. Majority drug molecules display poor solubility, which in turn affects the overall bioavailability of the molecule[1]. When dissolution is rate limited, the buccal delivery of such drug candidates is a tedious task[2]. There are number of methodologies which can be targetted for solubility enhancement, such as salt formation, use of cosolvents, particle size reduction, inclusion complexes of cyclodextrins etc[3-12]. Above all these, fabrication of solid dispersions can serve both the purposes of solubility and dissolution enhancement. These systems have aced in the domain of solubility enhancement, as they surpass the obstacles of the ancient methods. But the real success depends on the carrier selection and its optimization. When such systems come in contact with water, carrier is eroded and drug is set free as a fine colloidal dispersion with exorbitant surface area rendering elevated rates of drug dissolution and biological availability. In relation to all above, a modification from crystallin to amorphous form takes place, which is valuable as dissolution of an amorphous drug is simple and do not need any energy to fragment the crystalline structure[13,14].

Lercanidipine hydrochloride chemically is 2[(3,3-diphenylpropyl) (methyl)amino]-1, 1-imethylethyl methyl 2,6- dimethyl-4- (3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate hydrochloride. It is reported in 1, 4-dihydropyridine calcium channel blockers pharmacological class[15]. It is a BCS class II drug with low aqueous solubility and bioavailability. So improvement of the drug bioavailability and therapeutic efficacy is a crucial parameter which can only be achieved by increasing the solubility. The main goal is to work on the solubility enhancement by dispersing the drug in the polymer matrix of PVP and Guar Gum in different ratios. Melt fusion method is used for the preparation of solid dispersion and preliminary screening for polymer selection is performed. As oral route being the most suitable route of administration has become a vital

component nowadays, so work has been undertaken to develop a fast dissolving system, which disintegrates and disperses the drug in few seconds and can be conveniently administered. Finally, these solid dispersions were incorporated into fast disintegrating tablets which were further evaluated.

MATERIALS

Lercanidipine hydrochrloride was received as a free gift sample from Torrent Pharmaceutical Pvt. Limited, Baddi, Himachal Pradesh, India. Polyvinyl pyrollidine (PVP-K30) and Guar Gum was purchased from local vendor. Other materials used were of analytical grade.

EXPERIMENTAL

Solubility study

Solubility studies of lercanidipine hydrochloride were checked in water, phosphate buffer pH 6.8, HCl buffer pH 1.2 and phosphate buffer pH 7.2. The saturated solutions were prepared by adding excess drug in the solvent system. The solvent system was shaken for 48 hrs at 25^{0}C. Filtered the solutions through a 0.42 Millipore filter. Samples were analysed by UV spectrophotometer 236 nm. The solubility data is reported in table 1[16].

Table 1: Solubility of lercanidipine HCl in various solvent

Solvents	Solubility (mg/ml)
Water	0.014±0.002
Phosphate buffer pH 6.8	0.005±0.001
0.1 N HCl	0.160±0.012
Phosphate buffer pH 7.4	0.004±0.015

Preliminary attempts for the screening of polymers for solid dispersion preparation

The success of a solid dispersion system is rooted on the type and concentration of polymer. Various polymers were scrutinized for the enhancement of solubility. Solid dispersions were prepared with melt fusion method. Drug was mixed with Polyvinyl pyrollidine (PVP K-30) (LS-1 to LS-3) and Guar Gum (LS-4 to LS-6) in various ratios. The melt was evaporated in a water bath at 70°C. Then immediately solidified the mixture in ice bath with uninterrupted stirring[17,18].

Evaluation of Solid dispersions

Solubility studies

The solubility study of various Solid dispersions batches was determined in phosphate buffer pH 6.8. Weighed amount of solid dispersion equivalent to drug dose was added in excess quantity of solvent in screw-capped glass vials. The vials were continuously shaken for 2 hours. Finally the solutions were filtered and analysed spectrophotometrically at 236 nm.

Table 2: Solubility data of preliminary solid dispersion batches

Formulation Code	Solubility (mg/ml)
LS-1	0.347±0.08
LS-2	0.655±0.01
LS-3	0.801±0.07
LS-4	0.878±0.01
LS-5	0.941±0.08
LS-6	0.798±0.09

Infra red Spectral analysis

FT-IR spectrum of pure Lercanidipine hydrochloride and batch LS-5 is shown in Figure 1 and Figure 2 respectively. The IR spectra of Lercanidipine hydrochloride exhibited distinctive peaks at 3443 cm-1 stretching, 1649 cm-1 Amides (RCONH2), 1521 cm-1 Aromatics (C-C ring). The FTIR spectra of LS-5 displayed same characteristic peaks which also reveals that the drug and excipients used in the formulation are stable and posses no interaction[19,20].

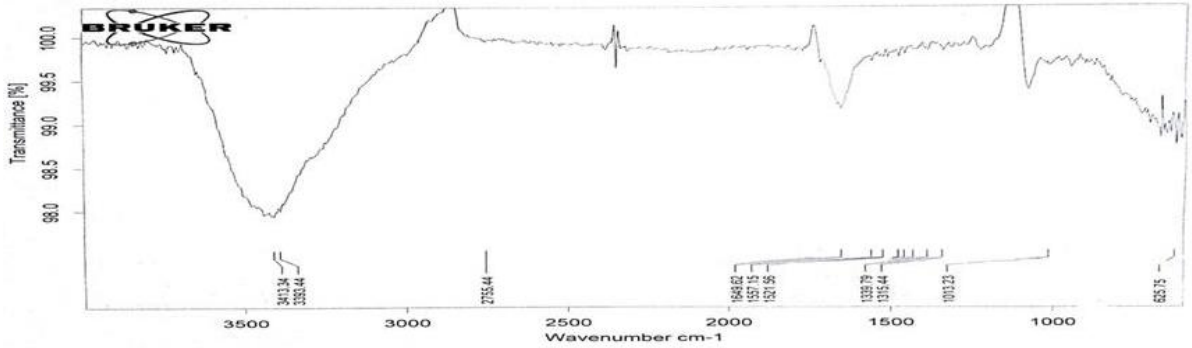

Figure 1: FTIR Spectra of Lercanidipine Hydrochloride

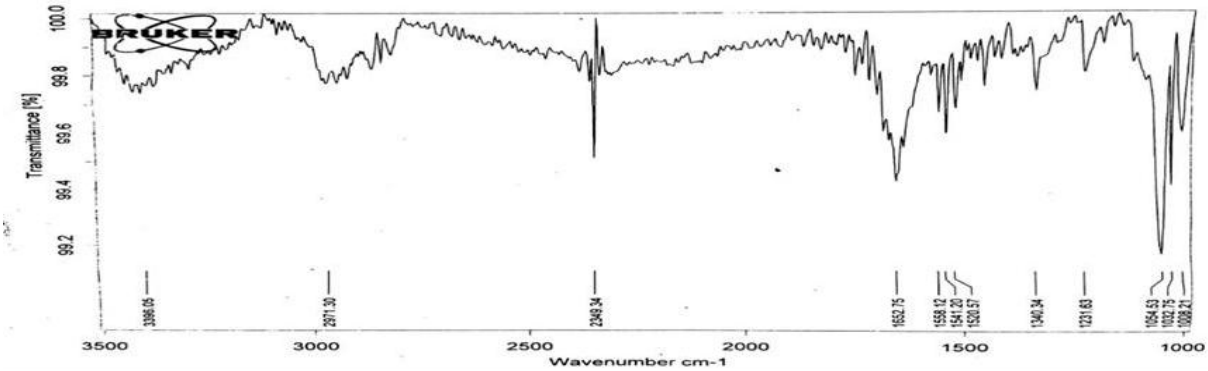

Figure 2: FTIR Spectra of batch LS-5

Differential scanning calorimetry

The DSC studies were conducted using DSC-60 instrument (Schimadzu corporation Japan). The samples of pure drug and batch LS-5 were sealed and heated at a constant rate at 50ºC/min over a temperature range of 25-175ºC. Inert atmosphere was created by introducing nitrogen gas at 50 ml/mins flow rate[21,22]. DSC thermographs melting endothermic at 179.7^{0}C (172^{0}C-183^{0}C) at 88.97 J/g i.e. melting point and crystalline state of drug. DSC thermograph of LS-5 is shown in Figure 4 which shows no peak i.e. melting point and amorphous state of drug. Disappearance of the drug melting peak confirmed that amorphization had occured.

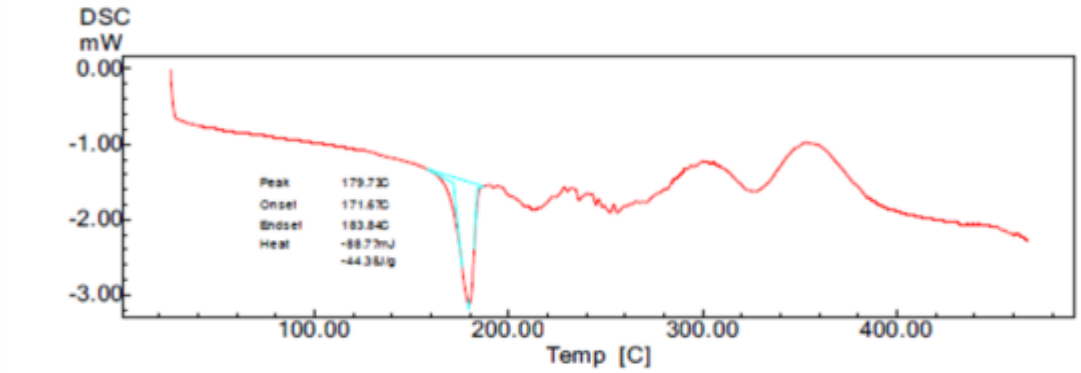

Figure 3: DSC of Lercanidipine hydrochloride

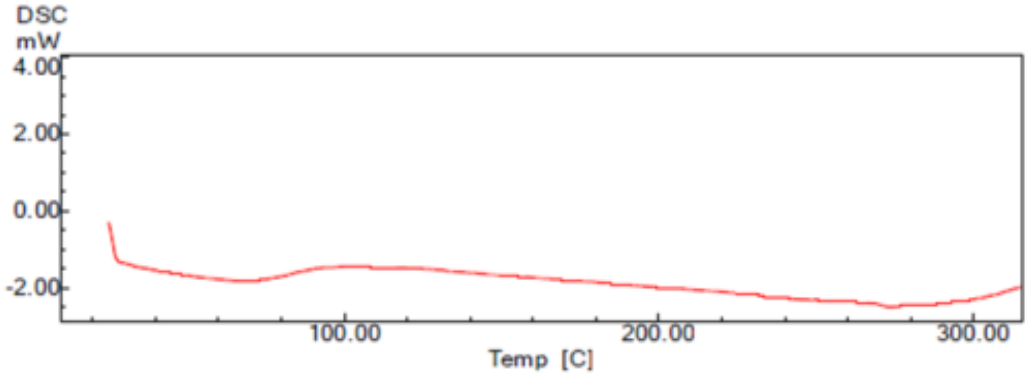

Figure 4: DSC of batch LS-5

Scanning electron microscopy

The drug and batch LS-5 were examined for surface changes using scanning electron microscope as shown in figure 5 and figure 6 respectively. Finally surface topography was studied[23].

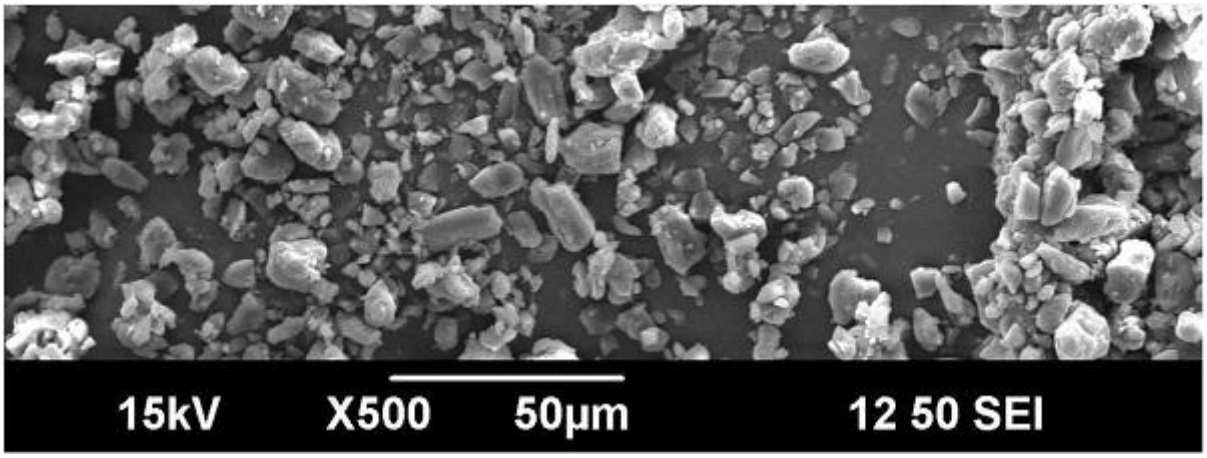

Figure 5: SEM image of the Lercanidipine Hydrochloride

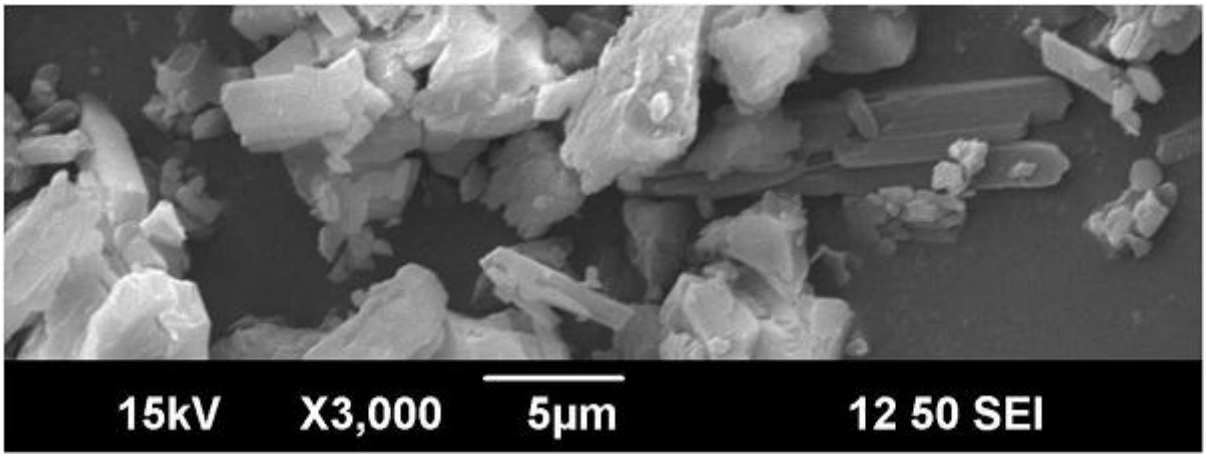

Figure 6: SEM image of batch LS-5

Experimental Design

A three- level, two factor experimental design was choosen for the study as shown in Table 3. The table indicates the ratios of independent variables, Lercanidipine Hydrochloride (A) and screened polymer Guar gum (B). The solubility and drug content, was selected as dependent variables. Response surface methodology computations were performed using Design Expert Software version 11. Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis approach. In addition contour and surface plots were also obtained to represent the effect of independent variables graphically.

Preparation of Lercanidine Hydrochloride Fast disintegrating Tablets containing superdisintegrants

Different batches of fast disintegrating tablets of Lercanidipine hydrochloride containing best optimized solid dispersion batch (OLS-1) were prepared according to the proportions given in Table 3. Powdered solid dispersion batch (OLS-1) equivalent to 10 mg of LR, was mixed with other excipients. Finally tablets were compressed on a rotary punch tablet machine (Karnavati, Mumbai, India) keeping final weight of the tablet (100 mg) [24,25].

Table 3: Optimization parameters of Guargum loaded solid dispersion

Run	Dependent variables		Independent variables	
	Factor 1	Factor 2	Response 1	Response 2
	A:Drug conc.(mg)	B:Polymer conc.(mg)	Solubility(µg/ml)	% drug release in 60 mins(%)
OLS-1	300	400	0.941	98
OLS-2	441.421	400	0.88	98
OLS-3	300	682.843	0.941	85
OLS-4	200	200	0.789	80
OLS-5	158.579	400	0.699	98
OLS-6	400	200	0.87	80
OLS-7	400	600	0.87	87
OLS-8	300	117.157	0.941	63
OLS-9	200	600	0.789	87

Table 4: ANOVA for Quadratic model Response 1: Solubility

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	0.0718	5	0.0144	27.45	0.0002(Significant)
A-Drug conc.	0.0218	1	0.0218	41.77	0.0003
B-Polymer conc.	1.388E-17	1	1.388E-17	2.654E-14	1.0000
AB	0.0000	1	0.0000	0.0000	1.0000
A^2	0.0499	1	0.0499	95.42	< 0.0001
B^2	0.0006	1	0.0006	1.06	0.3369
Residual	0.0037	7	0.0005		
Lack of Fit	0.0037	3	0.0012		
Pure Error	0.0000	4	0.0000		
Cor Total	0.0754	12			

Table 5: ANOVA for Quadratic model Response 2: Drug content

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	1370.59	5	274.12	39.08	< 0.0001(Significant)
A-Drug conc.	0.0000	1	0.0000	0.0000	1.0000
B-Polymer conc.	254.39	1	254.39	36.26	0.0005
AB	0.0000	1	0.0000	0.0000	1.0000
A^2	2.72	1	2.72	0.3874	0.5534
B^2	1108.80	1	1108.80	158.06	< 0.0001
Residual	49.11	7	7.02		
Lack of Fit	49.11	3	16.37		
Pure Error	0.0000	4	0.0000		
Cor Total	1419.69	12			

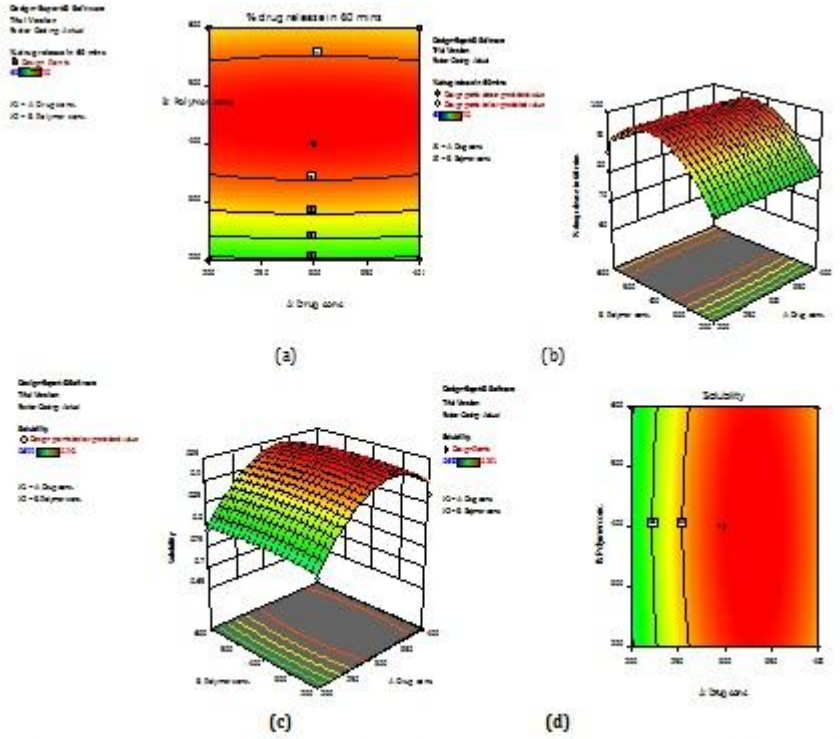

Figure 7: Images of contour plots (a,d) and three dimensional surface response plots (b,c) showing solubility and drug content as a function lercanidipine and polymer concentration.

Table 6: Composition of Fast Disintegrating Tablet

Formulation Code	Ingredients in mg					
	LT-1	**LT-2**	**LT-3**	**LT-4**	**LT-5**	**LT-6**
LS equivalent to 10 mg	50	50	50	50	50	50
Crosspovidone	2	4	6	-	-	-
Croscarmellose	-	-	-	2	4	6
Avicel pH 102	45	43	41	45	43	41
Magnesium stearate	1	1	1	1	1	1
Talc	2	2	2	2	2	2
Total weight	100	100	100	100	100	100

Pre compression parameters

Angle of repose: Accurately weighed quantity of the powder mixture was allowed to freely flow on to a surface from the funnel fixed at an appropriate height. The diameter is noted down. Finally angle of repose was calculated by using the following equation.

$$\tan \theta = h/r \quad (1)$$

Where θ is angle of repose, h is height of the cone and r is radius of the cone base.

Bulk density: Accurately weighed quantity of blend was added to a graduated cylinder and the bulk volume was measured using equation 2.

Bulk density = weight of the powder / bulk volume (2)

Tapped density: Accurately weighed quantity of blend was added to a graduated cylinder and the bulk volume was measured using equation 3.

Tapped density = weight of the blend / final volume (3)

Compressibility index: The compressibility index (Carr's index) indicates the property of a powder to be compressed and can be calculated using equation 4.

Carr's compressibility index =

[(Tapped density- bulk density/tapped density)] × 100 (4)

Table 7: Data for Precompression parameters

Formulation Code	Angle of Repose(º)	Bulk Density(g/cc³)	Tapped Density (g/cc³)	Compressibility Index (%)
LT-1	23.7±0.14	0.42±0.12	0.58±0.17	27.58±0.18
LT-2	24.7±0.02	0.41±0.15	0.66±0.05	37.87±0.61
LT-3	24.8±0.08	0.43±0.08	0.55±0.09	21.81±0.09
LT-4	23.2±0.15	0.51±0.07	0.65±0.18	22.95±0.07
LT-5	23.1±0.20	0.45±0.71	0.59±0.23	23.72±0.15
LT-6	22.8±0.02	0.44±0.45	0.62±0.05	32.25±0.21

Post compression parameters

Evaluation of Fast Disintegrating Tablets

The tablet batches were evaluated for weight variation, friability, hardness, thickness, uniformity of weight, disintegration time, wetting time, drug content and *in vitro* dissolution study.

Weight variation

Average weight of 20 tablets was determined and then the individual tablet weight was compared with average weight as shown in table 8.

Friability

The tablets were weighed (Winitial) and placed in friabilator (Biolinkz, India). The appratus was operated at 25rpm for 4 minutes. Finally the tablets were dedusted and weighed again (Wfinal). The data is reported in table 8.

$$F = \frac{\text{Winitial - Wfinal}}{\text{Wfinal}} \times 100 \quad (5)$$

Hardness

Pfizer Hardness tester was used to check the hardness expressed in kg/cm². The data is shown in table 8.

Wetting time

For the determination of wetting time, tissue paper was soaked with 10 ml of water. Tablet was kept over the wet surface and noted down the time required for water to reach at the top of the tablet. The data is reported in table 8.

Disintegration Test

The Disintegration test apparatus was used to calculate the disintegration time and data is reported in table 8.

Determination of drug content

Ten tablets were powdered and the blend equivalent to 10 mg of LR was weighed and dissolved in phophate buffer pH 6.8. The solution was then filtered, diluted and drug content was determined by spectrophotometer at 236 nm[26-28]. The data is recorded in table 8.

Table 8: Data for the post compression parameters

Batch	Weight variation(mg)	Friability (%)	Hardness (Kg/cm²)	Wetting time(Sec)	Disintegration time(Sec)	Drug content (%)
LT-1	99.1±0.39	0.62±0.87	2.8±0.21	44±0.81	55±0.18	98±0.91
LT-2	98.4±0.78	0.77±0.55	2.5±0.76	37±0.77	45±0.33	99±0.87
LT-3	99.8±0.55	0.75±0.49	2.9±0.86	25±0.52	37±0.56	99±0.11
LT-4	99.3±0.37	0.88±0.99	3.0±0.12	35±0.28	47±0.61	98±0.37
LT-5	99.3±0.84	0.85±0.89	2.3±0.11	26±0.34	40±0.37	99±0.27
LT-6	99.4±0.86	0.71±0.77	2.2±0.85	19±0.43	30±0.81	99±0.71

***In-vitro* dissolution study**

Dissolution studies were conducted in a beaker having 30 ml phosphate buffer pH 6.8 which was maintained at 37 ± 0.50 °C. The assembly was placed on a magnetic stirrer and samples were drawn at appropriate time periods with replacement. The aliquots were filtered, diluted and analyzed by spectrophotometerically at 236nm[29].

***In vivo* study deign study**

The *in vivo* study procedure (Protocol approval number: RIP/IAEC/2018-19/02) was approved by the Institutional Animal Ethics Committee. Male rabbits (New Zealand) were choosen for the pharmacokinetic data collection. Rabbits (weighing 2.6–3.1 kg) were fasted overnight before the study plan proceeded. Divided the rabbits into two groups. One group received the marketed formulation (Lercanidipine hydrochloride equivalent to 3 mg/kg) whereas the other group received optimized fast disintegrating tablet batch LT-6. Tablet to be tested was kept on the tongue of the rabbit. This has been achieved with the help of body restraint device. Initially the mouth was wetted with water and then tablet was placed on the tongue[30-32]. Blood samples were withdrawn from the peripheral vein of each rabbit at appropriate interval of 0, 1, 2, 3, 4, 5, 7, 9, 12, 24 hrs.

The samples were centrifuged at 2000 rpm for 20 min. The clear supernatant serum layer was harvested and stored at -40 °C. Frozen samples were thawed at ambient temperature (25±2 °C) for at least 60 m. Serum samples were appropriately diluted with acetonitrile, vortexed and finally centrifuged again. Mixed Lercanidipine HCl with protein free plasma. From this 20µl was injected into an isocratic HPLC with UV detector. The column employed for the study was C18 (250 x 4.6mm, particle size: 5µm, High pressure gradient, Detector : UV Wavelength:240nm). Potassium dihydrogen orthophosphate: ACN pH 4(40:60) was used as mobile phase with a flow rate upto 1.0 ml/min. Various

pharmacokinetic parameters such as peak plasma concentration (Cmax), the time at which peak occurred (tmax) and area under the curve (AUC) were computed from time v/s serum drug concentration values.

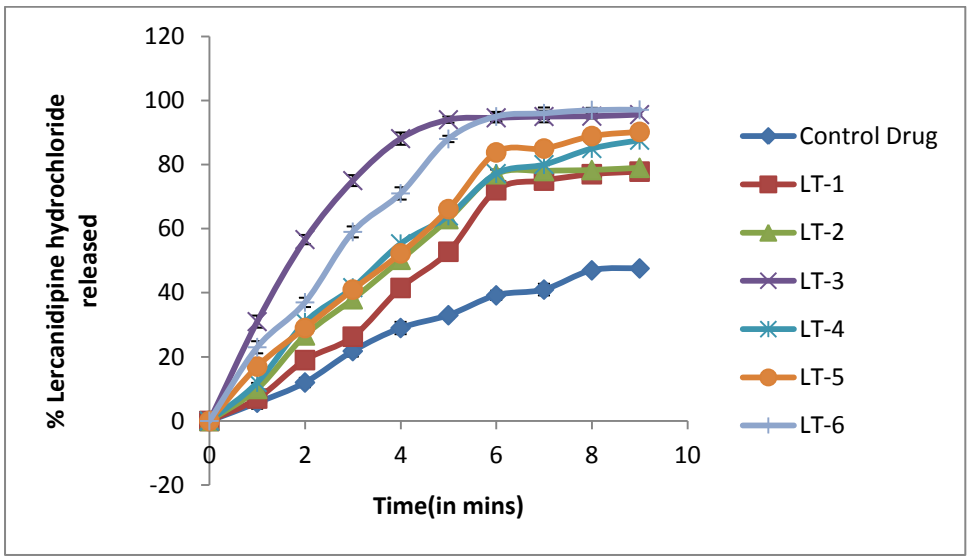

Figure 8: Dissolution release profile of FDT Tablet batches (LT-1 to LT-6)

Table 9: Pharmacokinetic parameters following after oral administration.

Pharmacokinetic parameters	Optimized Formulation LT-6	Marketed Preparation
C_{max}	20.11	16.31
T_{max}	3hr	4hr
AUC	230	205

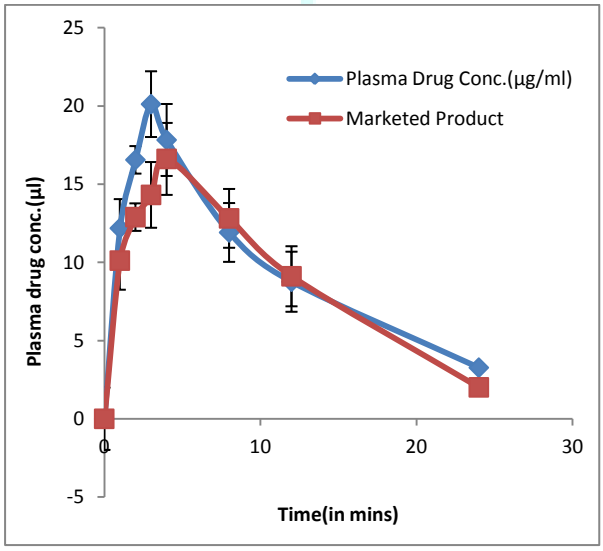

Figure 9: The pharmacokinetic profile of optimized FDT and marketed product.

Stability Studies

The best formulation batch was charged for the stability study as per ICH guidelines. They were performed at temperature of 40+2^{0}C / 75% RH for 3 months. LT-6 batch was charged for the study. It was wrapped in a butter paper followed by aluminum foil and sealed in an air-tight plastic pouch. The samples were checked for *in vitro* disintegration time and drug content for 30 days, 60 days and 90 days after storage[33].

Table 10: Stability data of the optimized batch LT-6 batch

Evaluation Parameter	Duration			
	0 days	30 days	60 days	90 days
Disintegration Time (Sec)	30±0.37	30±0.27	30±0.87	30±0.07
Drug Content (%)	99.42±0.39	99.15±0.45	99.12±0.67	99.10±0.81

DISCUSSION

The solubility and dissolution rate of Lercanidipine hydrochloride has been improved by formulating a solid dispersion with PVP-K30 and Guargum in the preliminary screening for polymer (Batch LS-1 to LS-6). Various natural and synthetic polymers are used in the preparation as they are economical, readily available, non-toxic, biodegradable and biocompatible. The solubility results are reported in table 1.

After the preparation of solid dispersions, solubility determination is an important factor which affects the dissolution pattern. The solubility study confirmed that LS-5 exhibited maximum solubility. Also it was revealed that Guargum showed much enhanced solubility as compared to other carrier. It was observed, that on increasing the polymer concentration, there was a sharp increase in solubility upto a point than further decreased, which can be attributed to the fact that as the polymer concentration increases, polymer gets adsorbs on the surface of drug, which retards the drug dissolution in the long run.

The FTIR spectra of pure drug and solid dispersion batch LS-5 displayed same characteristic peaks and revealed no chemical interaction between the drug and excipients as depicted in figure 1 and figure 2 respectively. Thermograms of drug and batch LS-5 are depicted in figure 3 and figure 4 respectively**.** DSC reports also reveals that the disappearance of the drug melting peak is a result of amorphization as shown in figure 6. The reduction in drug peak height and its broadening can be considered as a result of the change in the crystalline state to amorphous one. SEM photographs are shown in figure 5 and figure 6.

Optimization of independent variables outlined that solid dispersion prepared with drug: guargum (1:2 ratio) showed maximum solubility of 0.941±0.08 mg/ml. Based on this result, guargum polymer was selected for further formulation studies.

Optimization of dependent variables, ANOVA was used for predicting the significance ($p < 0.05$) of the model and individual response parameters. The various plots were scrutinized to check the impact of independent factors on the measured responses. The quadratic model of F-value 27.45 implies the model is significant $p < 0.05$. The contour plot and surface response plot in figure 7 showed the effect of different independent variables on solubility. The solubility of solid dispersion increased as the amount of guargum also increased, but to a certain level then decreased abruptly.

Response 2 (% Drug release at time 60 mins Y2), After ANOVA estimation, the quadratic model of F-value 39.08 implies the model is significant $p < 0.0001$. The various plots in figure 7 showed the effect of different independent variables on drug release at 60 min. The maximum drug release was obtained upto polymer concentration of 400 mg and further increase decreases the % drug release. This increase in rate of drug dissolution could be because of the dispersion of drug in pores of guargum and increased wettability. The dissolution rate showed a sharp rise at 1:2 ratio, but then decreased at higher values. This is attributed to the fact that there is firm adsorption of the drug on polymer, which retards the dissolution process of the drug.

Fast disintegrating tablets were prepared by direct compression method using optimized Lercanidipine Solid Dispersion (OSD-1), various super disintegrants crospovidone and croscarmellose are used and evaluated.

Total of six formulations LT-1 – LT-6 with fixed concentration of different super disintegrants were prepared as shown in table 5. Weight variation for all batches was within the range prescribed for uncoated tablets. Friability was reported within 0.62 to 0.88% and hardness within 2.2 to 3.0 kg/cm^2 range. The wetting times and disintegration time was within 19 to 44 secs and 30 to 55 secs respectively. The accreditation for fast wettability and disintegration could be assigned to the capillary action mechanism of the superdisintegrant which leads to fast puffiness of the dosage form. The drug content was found to be between 98 – 99 % which was within the acceptable limits.

Among all formulations LT-6 showed maximum 97.6 % drug release within 10 min. This may be credited to the brisk dissolution of the tablet, which is due to the usage of super disintegrant and carrier all together in the formulations. The results showed that FDT formulated using croscarmellose sodium with concentration up to 6 % showed better results than FDT formulated with crospovidone.

Finally LT-6 formulation was tested for stability at 25°C/65% and 40°C/75% RH for a period of 3 months. The tablets were once more evaluated for drug content and *in vitro* disintegration time. At last, no modifications in the disintegration time and drug content of tablets were seen.

CONCLUSION

The above carried research work revealed that the solid dispersion technique could be a lucrative way for solubility enhancement of Lercanidipine hydrochloride, using Poly vinyl pyrollidine (PVP K-30) and guargum as carriers. From the preliminary screening for polymer, Guargum was selected for the further formulation studies. Optimized guargum solid dispersion was finally incorporated into FDT. The FDT were formulated by direct compression method, having crospovidone and croscarmellose as superdisintegrant. Batch LT-6 showed maximum 97.6 % drug release within 10 min. At last, it is summarised that fast disintegrating tablet formulation can be an innovative and promising approach for the delivery of Lercanidipine Hydrochloride with enhanced dissolution and bioavailability, and also as an effective therapy for the treatment of hypertension.

ACKNOWLEDGMENTS

The authors are gratified to Glenmark Pharmaceutical Ltd., Baddi, Nalagarh (Himachal Pradesh) for providing free gift samples of Lercanidipine hydrochloride. The authors also appreciate the efforts of Signet Chemicals Ltd., Mumbai, for the gift sample of crosspovidone and crosscarmellose.

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