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SOLUBILITY ENHANCEMENT AND OPTIMIZATION OF VARIOUS VARIABLES OF FAST DISINTEGRATING TABLETS OF LERCANIDIPINE HYDROCHLORIDE USING CENTRAL COMPOSITE DESIGN

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Keywords:

Lercanidipine hydrochloride, Solid dispersion, Statistical design approach, Solvent evaporation method, Kneading method, Fast disintegrating tablet, *In-vivo* studies

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ABSTRACT: The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion, but it is problematic if the drug is poorly soluble. Sufficient drug absorption, reproducible bioavailability and pharmacokinetic profile of orally administered drug substances are highly dependent on the solubility of that compound in an aqueous medium. Also, the therapeutic effectiveness of drugs depends upon bioavailability and, ultimately, upon the solubility of drug molecules. Solid dispersions have attracted considerable interest as an efficient means of improving the solubility and hence bioavailability of a range of hydrophobic drugs. These systems are one of the most promising approaches for solubility enhancement. They are referred to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug (1-4). The aim of the present study was to improve the solubility and dissolution rate of Lercanidipine Hydrochloride (L) by formulating a solid dispersion with Polyvinyl pyrollidone (PVP-K30) and Guar gum. Central composite design (CCD) was employed using Design-Expert software version 12 to prepare optimized fast disintegrating tablets of Lercanidipine Hydrochloride.

INTRODUCTION: The most simple, easy, and convenient path of drug administration is through the oral route due to its better stability, dose accuracy, lesser bulk, and easy manufacturing [1, 2]. Improvement in drug solubility and, in turn, the oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development.

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The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general, include micronization, salt formation, use of surfactant, and use of pro-drug. However, all these techniques have potential limitations [3-4].

Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility, and oral absorption of poorly water-soluble drugs. SD is now firmly established as a platform technology for the formulation of drug delivery systems of poorly water-soluble agents [5-6]. The term solid dispersions have been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to

enhancing the oral bioavailability. Chiou and Riegelman defined these systems as the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method [7].

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. 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 that can only be achieved by increasing the solubility [8, 9]. The aim of the present research work is to increase the solubility and dissolution rate of Lercanidipine hydrochloride by forming solid dispersions using polymers PVP K-30 and Guar Gum in different ratios, and also employing two different methods for their preparation. Then work had been undertaken to optimize the fast disintegrating tablets using central composite design [10-14].

MATERIALS AND METHODS:

Materials: Lercanidipine Hydrochloride was received as a free gift sample from Cipla Pvt. Limited, Baddi, Himachal Pradesh, India. Polyvinyl pyrollidone (PVP-K30) and Guar Gum was purchased from a local vendor. Other materials used were of analytical grade [15].

Solubility Study: Solubility studies of Lercanidipine Hydrochloride were checked in various solvents water, phosphate buffer pH 6.8, and HCl buffer pH 1.2. The saturated solutions were prepared by adding excess drug in the solvent system. The solvent system was shaken for 48 h at 25 ºC. Filtered samples were analyzed by UV spectrophotometer at 236 nm. The solubility data is reported in **Table 1** [16].

TABLE 1: SOLUBILITY OF LERCANIDIPINE HYDRO-CHLORIDE IN VARIOUS SOLVENTS

Solvents	Solubility (µg/ml)
Water	1.68±0.066
Phosphate buffer pH 6.8	5.18±1.671
0.1 N HCl	145±0.978

Preparation of Solid Dispersion: Solid dispersions were prepared with two different methods, Solvent Evaporation Method and Kneading Method using two polymers (PVPK-30 and Guar Gum) in order to study the effect of individual method or polymer on the final formulation.

Solvent Evaporation Method: Drug was mixed with PVPK-30(LP1 to LP4) and Guar Gum (LG1 to LG4) in the ratios of 1:1 to 1:4. The polymers were dissolved separately in an adequate amount of methanol. The solvent was then rapidly evaporated with the help of heat. The precipitate was crushed, sized, and stored in a desiccator, until further use [17, 18].

Kneading Method: A mixture of drug and polymer PVP-K30 (LP5 to LP8) and Guar gum (LG5 to LG8) was wetted with water and kneaded thoroughly for 30 min in a glass mortar. The paste formed was dried under vacuum for 24 h. The dried powder was passed through #60.

Evaluation of Solid Dispersions:

Solubility Studies: The solubility study of various Solid dispersions batches was determined in phosphate buffer pH 6.8. A weighed amount of solid dispersion equivalent to drug dose was added in an excess quantity of solvent in screw-capped glass vials. The vials were continuously shaken for 2 h. Finally, the solutions were filtered and analyzed spectrophotometrically at 236 nm.

TABLE 2: SOLUBILITY DATA OF SOLID DISPERSION BATCHES

Carrier	Drug : Carrier Ratio	Batch	Technique Used	Solubility (µg/ml)
PVP-K30	1:1	NP1	Solvent Evaporation Method	240
	1:2	NP2	Solvent Evaporation Method	361
	1:3	NP3	Solvent Evaporation Method	507
	1:4	NP4	Solvent Evaporation Method	518
	1:1	NP5	Kneading Method	197
	1:2	NP6	Kneading Method	303
	1:3	NP7	Kneading Method	469
	1:4	NP8	Kneading Method	480
	1:1	NG1	Solvent Evaporation Method	198

	1:2	NG2	Solvent Evaporation Method	315
	1:3	NG3	Solvent Evaporation Method	461
Guar Gum	1:4	NG4	Solvent Evaporation Method	478
	1:1	NG5	Kneading Method	165
	1:2	NG6	Kneading Method	291
	1:3	NG7	Kneading Method	411
	1:4	NG8	Kneading Method	419

Infra-Red Spectral Analysis: In FTIR study, the characteristic peak of Lercanidipine Hydrochloride has appeared in the spectra of a pure drug without any remarkable change in the position. It was confirmed that there was no chemical interaction between the drug and the polymer. The FTIR spectra of solid dispersion batch LP3 displayed the same characteristic peaks, which also reveals that the drug and excipients used in the formulation are stable and posses no interaction [19, 20].

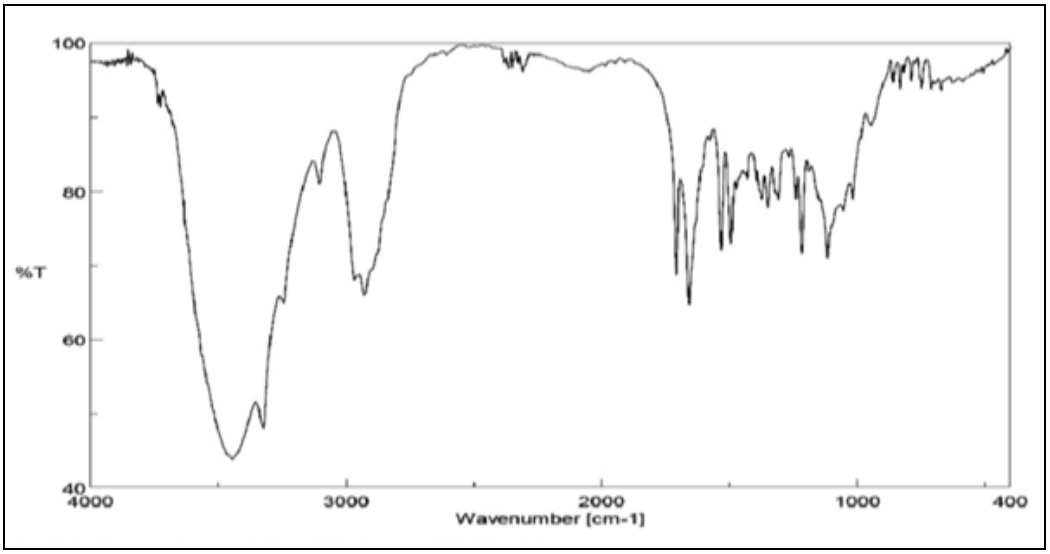


FIG. 1: FTIR SPECTRA OF LERCANIDIPINE HYDROCHLORIDE

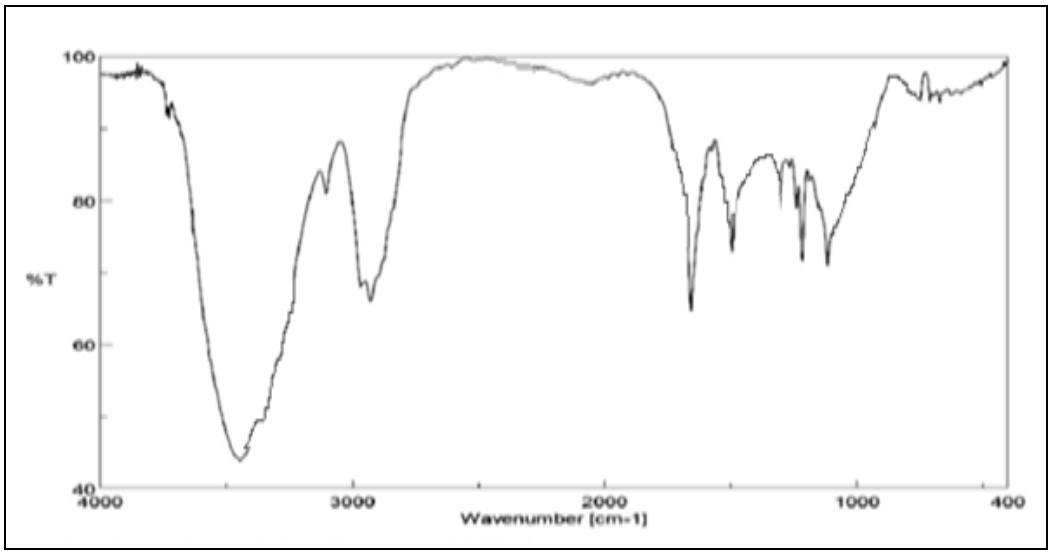


FIG. 2: FTIR SPECTRA OF BATCH LP3

Differential Scanning Calorimetry: The differential scanning calorimetry experiment was performed on the drug and the solid dispersion batch LP3. The samples were analyzed by DSC analyzer. The DSC thermogram of pure Lercanidipine Hydrochloride showed a sharp endothermic peak at 179.11°C, which was ascribed to drug melting. DSC thermograph of LP3 is shown in **Fig. 4,** which shows no peak *i.e.*, melting point and amorphous state of drug. The disappearance of the drug melting peak confirmed that amorphization had occurred [21-23].

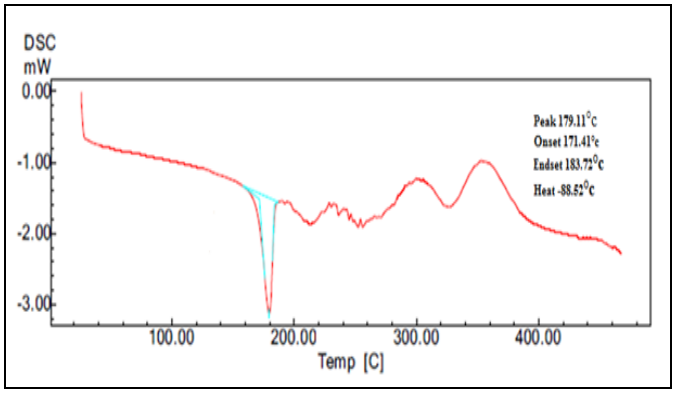


FIG. 3: DSC OF LERCANIDIPINE HYDROCHLORIDE

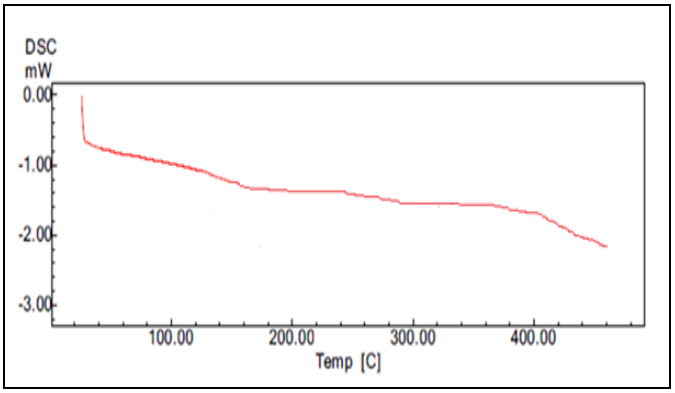
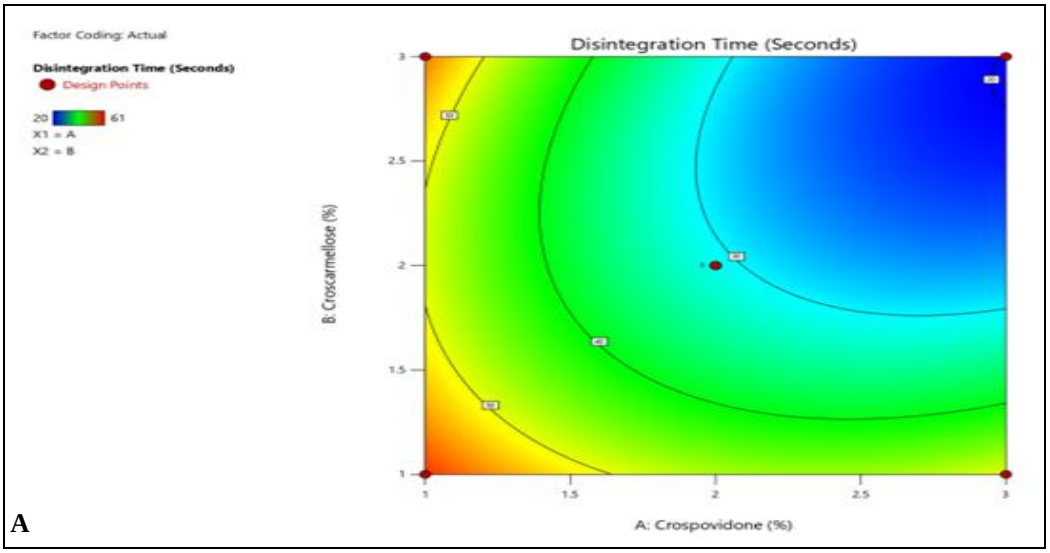
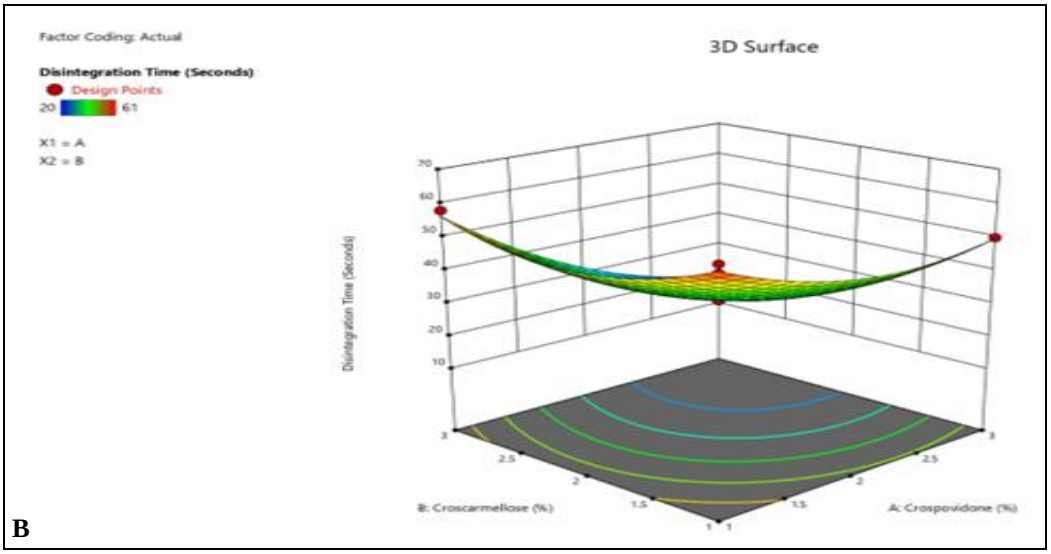


FIG. 4: DSC OF SOLID DISPERSION BATCH LP3

Experimental Design: Central composite design (CCD) was employed using Design-Expert software version 12 to prepare fast disintegrating tablets of Lercanidipine Hydrochloride. The independent variables selected were croscarmellose i.e. X1 (0.59-3.41% w/w) and crospovidone *i.e.* X2, (0.59-3.41% w/w). The response variables studied were friability and disintegration time. Response surface methodology was adopted to study the relationship between dependent and independent variables. The composition of all the nine formulations as designed by design expert software are summarized in **Table 3**[24, 25].



A



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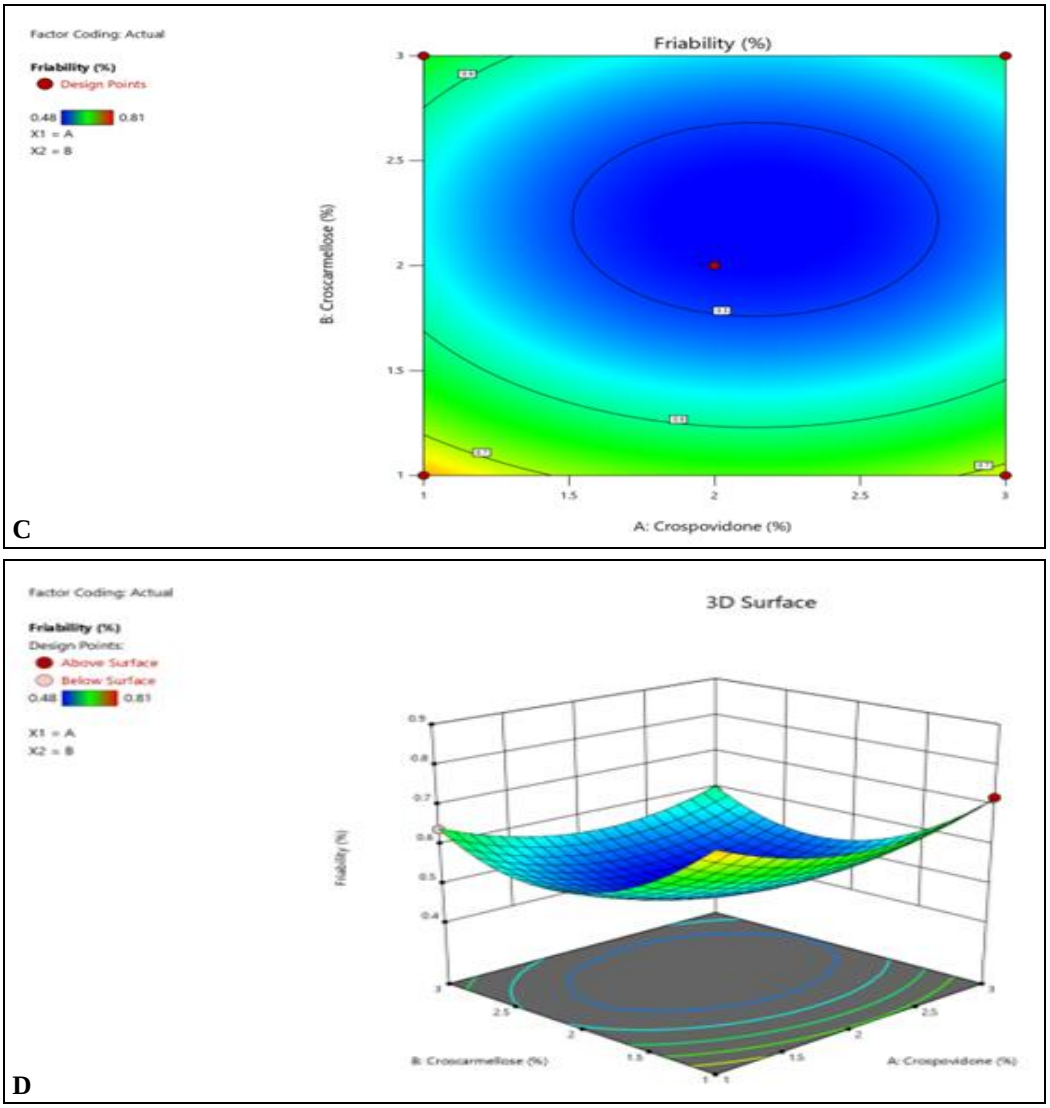

FIG. 5: IMAGES OF CONTOUR PLOTS (A, C) AND THREE DIMENSIONAL SURFACE RESPONSE PLOTS (B, D) SHOWING THE EFFECT OF CROSCARMELLOSE AND CROSPOVIDONE ON THE DISINTEGRATION TIME AND FRIABILITY OF FAST DISINTEGRATING TABLETS

Optimization of Formulation Variables: The optimized amount determined with the help of software is depicted in surface response curves, as shown in **Fig. 7**.

TABLE 3: CENTRAL COMPOSITE DESIGN WITH TWO FACTORS, NINE RUNS

Formulation code	Factor 1	Factor 2	Response 1	Response 2
	Crospovidone (%)	Croscarmellose (%)	Disintegration Time (Sec)	Friability (%)
LFT1	2	0.585786	58	0.81
LFDT2	2	2	31	0.58
LFDT3	3	3	20	0.59
LFDT4	0.585786	2	59	0.64
LFDT5	1	1	61	0.77
LFDT6	1	3	58	0.64
LFDT7	3	1	50	0.72
LFDT8	3.41421	2	29	0.6
LFDT9	2	3.41421	35	0.67

Analysis of Data by Design Expert Software: The analysis of variance (ANOVA) and multiple regression analyses were done using Stat-Ease Design Expert 12 software. The statistical treatment and interpretation of data were essential steps where the p-value indicated main effects on optimization of the formulation.

TABLE 4: RESULTS OF ANOVA FOR DISINTEGRATION TIME

Source	Sum of squares	df	Mean Square	F-value	p-value	
Model	2485.65	5	497.13	259.12	< 0.0001	significant
A-Crospovidone	1044.85	1	1044.85	544.62	< 0.0001	
B-Croscarmellose	536.72	1	536.72	279.76	< 0.0001	
AB	182.25	1	182.25	95.00	< 0.0001	
A^2	340.87	1	340.87	177.68	< 0.0001	
B^2	473.48	1	473.48	246.80	< 0.0001	
Residual	13.43	7	1.92			
Lack of Fit	13.43	3	4.48			
Pure Error	0.0000	4	0.0000			
Cor Total	2499.08	12				

TABLE 5: RESULTS OF ANOVA FOR FRIABILITY

Source	Sum of squares	df	Mean Square	F-value	p-value	
Model	0.1668	5	0.0334	325.87	< 0.0001	Significant
A-Crospovidone	0.0031	1	0.0031	29.94	0.0009	
B-Croscarmellose	0.0262	1	0.0262	256.18	< 0.0001	
AB	0.0000	1	0.0000	0.0000	1.0000	
A^2	0.0341	1	0.0341	333.05	< 0.0001	
B^2	0.1176	1	0.1176	1148.67	< 0.0001	
Residual	0.0007	7	0.0001			
Lack of Fit	0.0007	3	0.0002			
Pure Error	0.0000	4	0.0000			
Cor Total	0.1675	12				

Formulation of Optimized Fast Disintegrating Tablet: The tablets were prepared by direct compression method. Solid dispersion batch LP3 equivalent to 10 mg was weighed and added to the fast disintegrating tablet batch.

TABLE 6: COMPOSITION OF OPTIMIZED FAST DIS-INTEGRATING TABLET

Ingredients	Amount (mg)
Lercanidipine Hydrochloride SD (LP3) equivalent to 10 mg	40
Crospovidone	4.5
Croscarmellose	4.5
Avicel pH 102	qs 150
Magnesium stearate	3
Talc	3
Total weight	150

Evaluation of Optimized Fast Disintegrating Tablet: Various parameters like weight, hardness, friability, wetting time, disintegration time, and drug content were evaluated as shown in table.

TABLE 7: EVALUATION OF OPTIMIZED LFDT

Parameters	Optimized LFDT
Weight (mg)	149.94±1.89
Hardness (kg/sq.cm.)	2.1±0.87
Friability (%)	0.61±0.89
Wetting time (sec)	15±1.69
Disintegration time (sec)	25±0.75
Drug content (%)	98.89±0.95

Weight Variation: Average weight of 20 tablets was determined and then the individual tablet weight was compared with average weight as shown in **Table 7**.

Friability: The tablets were weighed ($W_{initial}$) and placed in friabilator. The apparatus was operated at 25 rpm for 4 min. Finally, the tablets were dedusted and weighed again (W_{final}). The data is reported in **Table 7**.

$$F = W_{initial} - W_{final} \times 100 / W_{final}$$

Hardness: Pfizer Hardness tester was used to check the hardness expressed in kg/cm^2. The data is shown in **Table 7**.

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 7**.

Disintegration Test: The Disintegration test apparatus was used to calculate the disintegration time and data is reported in **Table 7**.

Determination of Drug Content: Ten tablets were powdered, and the blend equivalent to 10 mg of Lercanidipine Hydrochloride was weighed and dissolved in phosphate 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 7**.

***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 [29-30].

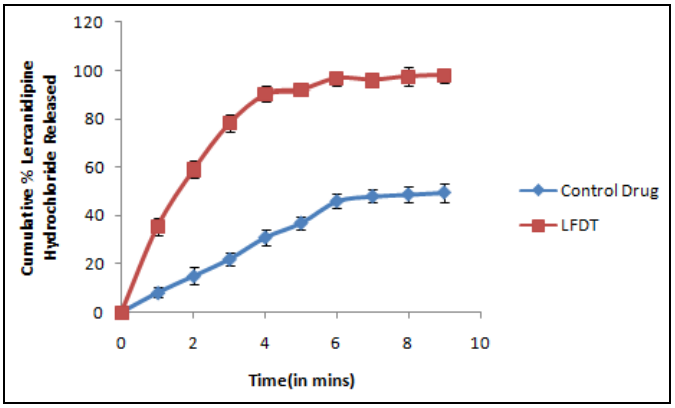

FIG. 6: *IN-VITRO* DRUG RELEASE DATA OF LFDT

DISCUSSION: In the present research work, solid dispersions were prepared with different methods and polymers in order to determine the effect of individual method or polymer on the final formulation. PVP-K30 and Guar Gum were used as polymers, respectively and their effect on solubility enhancement by formation of solid dispersions was checked. The solubility results are reported in **Table 1**.

Solid dispersions were prepared in different drug to polymer ratios ranging from 1:1 to 1:4 using Guar Gum and PVP-K30 as carriers. The data is given in **Table 2**. Solubility studies data revealed that PVP-K30 polymer increased the drug solubility to a greater extend than the Guar Gum polymer. Based on the solubility results, LP3 batch prepared with Solvent Evaporation Method with PVP-K30 as carrier has shown highest solubility of 507 µg /ml. On further increasing the drug carrier ratio upto 1:4 solubility increased to a non significant level. So, 1:3 drug carrier ratio was selected for further studies.

The FTIR spectra of pure drug and solid dispersion batch LP3 displayed same characteristic peaks and revealed no chemical interaction between the drug and excipients as depicted in **Fig. 1** and **Fig. 2** respectively. Thermograms of drug and batch LP3 are depicted in **Fig. 3** and **Fig. 4** respectively**.** DSC reports also reveals that the disappearance of the drug melting peak is a result of amorphization as shown in **Fig. 4**. 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.

Central composite design (CCD) was employed using Design-Expert software version 12 to check the effects of independent variables on the formulation properties of Fast Disintegrating Tablets. Response surface methodology was adopted to study the relationship between dependent and independent variables. The formulations (n=9) were designed by design expert having two independent variables, croscarmellose, and crospovidone concentration, respectively. The response variables studied were friability and disintegration time Adequacy and good fit of the models were tested using analysis of variance (ANOVA). Mathematical relationships generated for the studied response variables were expressed as equations for Disintegration time (X) and Friability (Y).

The following equations were generated when disintegration time was correlated with independent variables (A and B).

$$X = 31 - 11.43A - 8.19B - 6.75AB + 7A^2 + 8.25B^2 \quad .....(1)$$

The Predicted R^2 of 0.9618 is in reasonable agreement with the Adjusted R^2 of 0.9908; i.e., the difference is less than 0.2.

The equation generated that correlates friability with independent variables (A and B) is:

$$Y = 0.48 - 0.01A - 0.05B + 0.00AB + 0.07A^2 + 0.13B^2 \quad .....(2)$$

The Predicted R^2 of 0.9696 is in reasonable agreement with the Adjusted R^2 of 0.9927; *i.e.*, the difference is less than 0.2.

Both coefficients A and B bear a negative sign, as shown in equation 1, which indicates that on increasing the concentration of either super-disintegrant, crospovidone or croscarmellose, disintegration time decreases. This is due to the fact that the higher percentage of superdisintegrat induces higher porosity facilitating higher water uptake, which leads to reduced disintegration time. From equation 2, it is again evident that on

increasing the concentration of either super-disintegrants, the friability also decreases, and mechanically strong tablets were produced. RSM plots were constructed using a design expert to study the interaction between independent and dependent variables. The combined effect of croscarmellose and crospovidone on friability and disintegration time can be seen in **Fig. 5**. It is suggested that crospovidone and croscarmellose produced a combined effect of improving disintegration and dissolution. Both the disintegrants work well through swelling and capillary action.

The optimized Lercanidipine Hydrochloride fast disintegrating tablet LFDT was formulated, as shown in **Table 6**. The weight of the tablet batch LFDT was 149.94±1.89 mg. Friability was reported to be 0.61%±0.89 and hardness of 2.1±0.87 kg/cm^2. The accreditation for fast wet ability and disintegration could be assigned to the capillary action mechanism of the superdisintegrant, which leads to the fast puffiness of the dosage form. The drug content was found to be 98.89±0.95%. The wetting time and disintegration time were 15±1.69 and 25±0.75 sec, respectively. This may be credited to the brisk dissolution of the tablet, which is due to the usage of super disintegrant and carrier all together.

CONCLUSION: A fast and effective screening technique to develop stable solid dispersions for a poorly soluble drug is successfully developed. The research work revealed that the solid dispersion technique could be a beneficial way for solubility improvement, using Polyvinyl pyrrolidone (PVP K-30) and guar gum as carriers. From the preliminary screening for polymers, PVPK30 was selected for the further formulation studies.

Finally, Lercanidipine Hydrochloride Fast Disintegrating Tablets were successfully prepared to apply central composite design with the most appropriate combination of croscarmellose and crospovidone as super disintegrants. Batch LFDT was formulated with a maximum 97.89±3.21% drug release within 10 min. At last, it was summarised that fast disintegrating tablet formulation could 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.

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CONFLICTS OF INTEREST: The authors declare no conflict of interest.

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