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Formulation and Evaluation of Lercanidipine Hydrochloride by Liquisolid Technique

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ABSTRACT

The purpose of this study is to improve dissolution rate and solubility of water insoluble antihypertensive drug through its formulation into liquisolid tablets. The drug Lercanidipine HCL is BCS class II drug with10 % bioavailability. Attempt had made to investigate the use of liquisolid technique in improving the dissolution of lercanidipine hydrochloride in a solid dosage form. *In vitro* release pattern was studied using USP II apparatus. Different liquisolid tablets were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptable flowable and compressible admixture. Polyethylene glycol 400 is used as a non-volatile liquid vehicle. Avicel PH 102 and aerosil 200 were used as carrier and coating materials respectively to produce acceptably flowing powders which were compacted into tablets. The new mathematical model and 3^2 factorial design was utilized to formulate various liquisolid powder systems.The prepared liquisolid tablets were evaluated for their flow properties such as bulk density, tapped density, angle of repose, carr's index and hausner's ratio. By using Fourier Transform Infrared Spectroscopy (FT-IR), differential scanning calorimetry (DSC) and powder X- ray diffraction (PXRD) the interaction between drug and excipients in prepared liquisolid tablets were studied. The DSC and XRD studies confirm no significant interaction between drug and excipients used in liquisolid tablets.

1.0 INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects.[1] Dissolution is an important factor for absorption of drugs especially in case of water insoluble or poorly soluble drugs. The rate limiting step for most of the pharmaceutical formulations is dissolution.[2] Drugs with poor aqueous solubility will mainly exhibit dissolution rate limited absorption and drugs with poor membrane permeability will exhibit permeation rate limited absorption. Most promising NCE's, instead of their high permeability, are usually only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, which indicates that there is a small absorption window.[3]

This liquisolid technique was successfully applied for low dose water-insoluble drugs. Drug release is a crucial and rate limiting step for oral bioavailability, particularly for drugs with low solubility and high permeability i.e. BCS class II drugs. Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs or water insoluble solid drug dissolved in non-volatile solvent and this medication can be converted into free- flowing, non-adherent, dry looking, and readily compressible powders with the use of carrier and coating materials. In case of water soluble drugs, the sustained release can be obtained.[4]

Using this new formulation technique, a liquid may be converted into a dry-looking, non-adherent, free-flowing and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials.[5]

The good flow and compression properties of Liquisolid System (LS) may be attributed due to large surface area of silica and fine particle size of avicel. Hence LS compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics.

Lercanidipine hydrochloride is a calcium channel blocker. Its molecular formula is $C_{36}H_{41}N_3O_6HCl$ and molecular formula is 648 gm/mol. Lercanidipine is BCS class II drug. It has 8 to 10 hours half life with 10% bioavailability. Lercanidipine hydrochloride is used for treatment of hypertension and angina pectoris. Its poor aqueous solubility makes its absorption dissolution rate limited and thus delays the onset of action.Lercanidipine is a calcium antagonist of the dihydropyridine group and selectively inhibits the transmembrane influx of calcium into cardiac and vascular smooth muscle, with a greater effect on vascular

smooth muscle than on cardiac smooth muscle. The antihypertensive action is due to a direct relaxant effect on vascular smooth muscle which lowers total peripheral resistance and hence blood pressure.

2.0. MATERIALS AND METHODS

2.1 Materials:

Lercanidipine HCl was received from Glenmark ltd., Sinnar, Nashik, India. Polyethylene glycol 400 was received from LOBA Chemie, Mumbai. Avicel PH 102, Aerosil 200 and Sodium starch glycolate were received fromResearch- Lab Fine Chem. Industry, Mumbai.

2.2 Methods:

2.2.1 Solubility studies:

To select the best non-volatile solvent for dissolving or suspending of lercanidipine hydrochloride in liquid medication, solubility studies of lercanidipine hydrochloride were carried out in four different nonvolatile solvents, i.e. PEG 400, glycerin, polysorbate 80 and PG. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48hrs at 25^0C under constant vibration. After this period the solutions were filtered through a 0.42 Millipore filter, diluted with 0.1 N HCl and analysed by UV-spectrophotometer (Jasco v-630) at a wavelength of 241 nm against blank sample (blank sample contained the same concentration of specific solvent used without drug). Three determinations were carried out for each sample to calculate the solubility of lercanidipine hydrochloride.[6,7]

2.2.2 Preparation of Liquisolid tablets:

The desired quantity of the previously weighed solid Lercanidipine hydrochloride was dissolved in liquid vehicle (PEG 400). The solution was then sonicated for 15 min until a homogeneous drug solution was obtained. Next, the calculated weights (W) of the resulting liquid medications (equivalent to 10 mg drug) were incorporated into the calculated quantities of the carrier Avicel PH 102 and mixed thoroughly. The resulting wet mixture was then blended with the calculated amount of the coating material Aerosil 200 using a standard mixing process to form simple admixture. Finally 5% w/w of sodium starch glycolate was mixed with the above mixture for 10 min. The final blend of liquisolid powder system was

compressed into tablets of desired weight by using 10 station tablet compression machine (Rimek Mini Press II-DL Karnavati), directly compressed conventional tablets which are used for comparisons with liquisolid tablets is prepared by directly compressing powder mixture of lercanidipine hydrochloride with avicel PH 102, aerosil 200,and sodium starch glycolate [6]

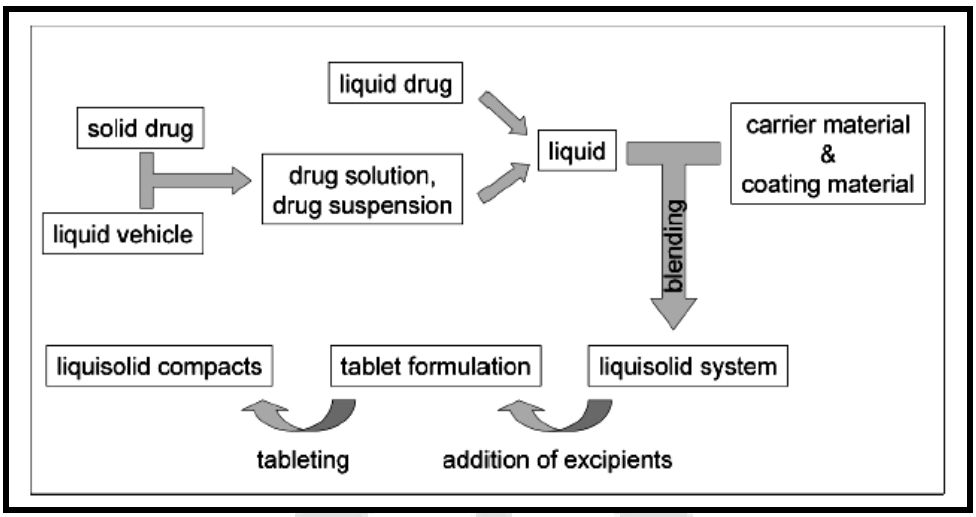

Figure 1: General method of preparation liquisolid systems

2.2.3 Calculation of liquid load factor (Lf))

It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). Different concentrations of nonvolatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended.

Lf=W/Q..... (1)[8]

W=ratio of weight of liquid medication

Q= weight of carrier material

The liquid load factor that ensures acceptable flowability

(Lf), and can be measured by:

The relationship between the powder excipients ratio (R) and liquid load factor (Lf) of the formulations can be given as follows:

$$Lf = \Phi + \varphi(1/R) \dots \dots \dots (2)^{9}$$

Where, Φ and *Φ*are the Φ-value of carrier and coat material respectively.

The optimum quantities of carrier (Q) and coating material

(q) were obtained from equation (3)

$$\mathbf{R = Q/q..... (3)}^{9}$$

q = Amount of coating material

2.2.4 Applications of the 3^2 factorial designs for designing of Lercanidipine hydrochloride liquisolid system:

Factorial design was employed for the preparation of the liquisolid tablets. Two independent factors are studied, each at three levels, and experimental trials are performed on all 9 possible combinations, PEG-400 (solubility enhancer): Avicel 102 (Carrier) is independent variables and cumulative drug release is dependent variable. The equation is

$$Y ¼ \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{11}X_{21} + \beta_{22}X_{22} + \beta_{12}X_1X_2$$

Where, Y is the measured response; X is the levels of factors; bis the coefficient computed from the responses of theformulations.

Table 1: 3^2 Full factorial Design Layouts

Sr. No.	Formulation Code	Coded Factor Levels with Combination	
		X1	X2
1	F1	50	250
2	F2	50	350
3	F3	50	450
4	F4	100	250
5	F5	100	350
6	F6	100	450
7	F7	150	250
8	F8	150	350
9	F9	150	450

Table 2: Composition of Lercanidipine hydrochloride liquisolid tablet as per Factorial Design

Ingredients	**Formulation code**								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Lercanidipine HCl	10	10	10	10	10	10	10	10	10
PEG – 400	50	50	50	100	100	100	150	150	150
Avicel PH-102	250	350	450	250	350	450	250	350	450
Aerosil-200	20	20	20	20	20	20	20	20	20
R*	12.5	17.5	22.5	12.5	17.5	22.5	12.5	17.5	22.5
Lf*	0.34	0.24	0.18	0.64	0.45	0.35	0.94	0.67	0.52
Total Weight (mg)	280	380	480	280	380	480	280	380	480

(5% Sodium starch is added)

3.0. Characterization of liquisolid formulations:

3.1. Flow properties of liquisolid system

The flow properties of the liquisolid systems were estimated by determining the angle of repose, carr's index, and hausner's ratio. The angle of repose was measured by the fixed funnel and free standing cone method.[6]The bulk density and tap densities were determined for the calculation of hausner's ratio and carr's index.

3.2. Fourier-transform infrared spectroscopy (FTIR)

FT-IR Spectrum of pure drug and drug-excipients were obtained by FT-IR Spectrophotometer (Bruker-Alpha).The spectrum of drug-excipient mixture so obtained were compared with spectrum of pure drug for any interactions.

3.3. Differential scanning calorimetry (DSC)

DSC was performed in order to assess the thermotropic properties by using differential scanning calorimetry (Shimadzu) About 3 mg of the sample were sealed in the aluminum pans and heated at the scanning rate of 10^0 C/min, flow rate is 50 ml/min. covering a temperature range of 10 to 500^0 C under nitrogen atmosphere.

3.5 Powder X-Ray Diffraction:

PXRD analysis was done by irradiating the samples with monochromatized Cu Kα radiation (1.506 Å) and analyzed between 3° and 60° (2θ) employing a PXRD spectrophotometer Rigaku miniflex 600, Rigaku co, Tokyo, Japan.

3.5 Evaluation of liquisolid tablets:

3.5.1. Hardness:

The hardness of liquisolid tablets was determined by using Monsanto hardness tester.

3.5.2. Thickness:

The thickness of liquisolid tablets was determined by using vernier caliper.

3.5.3 Weight Variation:

Weight variation was measured by weighing 20 tablets and average weight was found of the individual tablet should fall within specified limits.

3.5.4. Uniformity of content –

Ten tablets were powdered and blend equivalent to 10mg drug. It was dissolved in methanol and absorbance were taken at λmax 241nm. The tablet preparation complies with the test, only if each individual's content lies between 85 to 115% of the average content.

3.5.5. Friability Test –

As weight of tablet was less than 650 mg so tablets corresponding to 6.5 gm were taken for the test. All tablets were de-dusted carefully and after weighing accurately the required number of tablets were placed in the drum and rotated about 100 times at 25 rpm in friability

test apparatus. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss was calculated

$$\textbf{Friability} = \frac{\textbf{W1} - \textbf{W2}}{\textbf{W1}} \times \textbf{100}$$

Where,

W1 = weight of the tablets before test

W2 = weight of the tablets after test

3.5.6. Disintegration test:

One tablet was placed into each tube; the basket-rack assembly was suspended in the beaker containing distilled water at 37^0C ± 2^0Cand was operated without disc till all the tablets disintegrate. The time required for complete disintegration was recorded in triplet.

3.5.7. *In Vitro* Dissolution Studies:

The USP paddle apparatus was used for all the *in vitro* dissolution studies. 900ml 0.1N HCl was used as dissolution media, at 50 rpm and 37 ± 0.5^0C. Liquisolid tablets of lercanidipine of nine batches were added in 900 ml capacity jar of dissolution apparatus which paddle was rotated at 50 rpm. Appropriate aliquots were withdrawn at suitable time interval (10 to 120 min) and filtered through Whatman filter paper and diluted to 10 ml with 0.1N HCl. The samples were then analyzed at $\lambda_{max}$of 241 nm by UV/visible spectrophotometer.

3.5.8. Stability studies:

Stability study of formulation which gave maximum dissolution rate was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of optimized formulation was assessed at 40±2 ^{0}c/ 75±5% RH as per ICH Guidelines. 50 tablets equivalent to 380mg of Lercanidipine hydrochloride were filled with packed in aluminum foil and stored for 3 months. Samples were analyzed at 0, 30, 60, & 90 days for physical appearance, drug content, disintegration time, and hardness and *in-vitro* dissolution profile.

4.0 RESULT AND DISCUSSION

4.1 Solubility study:

As shown in Fig. 2the saturation solubility of Lercanidipine hydrochloride increases in the order of Polyethylene glycol 400 <Propylene glycol < Glycerin < Tween-80. Solubility of Lercanidipine hydrochloride was significantly increased in presence of Polyethylene glycol-400 i.e. 11.5 mg/ml. Polyethylene glycol- 400 was selected as a nonvolatile solvent in preparation of liquisolid tablets.

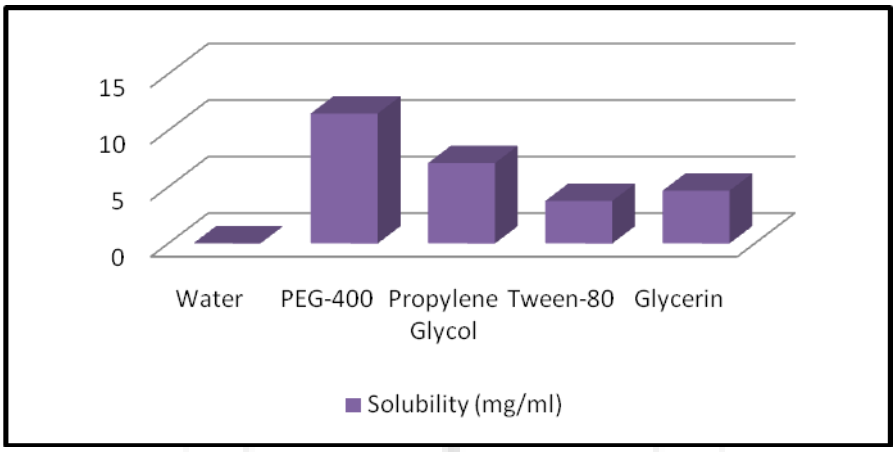

Figure 2: Solubility of Lercanidipine hydrochloride

4.2 Evaluation of flow properties of the Lercanidipine hydrochloride liquisolid system

Flow properties of the Lercanidipine hydrochloride liquisolid systemAngle of repose were found to be in the range of 27 to33 indicating acceptable flow properties .The percent compressibility for all formulations lie within the range of 10.32 ± 0.051to15.28 ± 0.052. Hausner's ratio was found to be in a range of 1.02 ± 0.016 to 1.17 ± 0.015(Table 3).

Table 3: Evaluation of liquisolid dried powder blend

Batch No.	Tapped density (gm/cm^3)	Bulk density (gm/cm^3)	Compressibility index (%)	Hausner's ratio	Angle of repose (ɵ)
F1	0.3755 ± 0.018	0.3284± 0.010	12.52 ± 0.026	1.143 ± 0.016	29.08 ± 1.41
F2	0.3401 ±0.004	0.3277± 0.010	15.28 ± 0.052	1.02 ± 0.025	27.46 ± 0.77
F3	0.3715 ± 0.011	0.3227± 0.011	10.49 ± 0.030	1.150 ± 0.15	31.57± 1.65
F4	0.3784± 0.018	0.3262± 0.010	13.77 ± 0.043	1.16 ± 0.025	29.90 ±2.21
F5	0.3574± 0.014	0.3335± 0.012	13.22 ± 0.020	1.07 ± 0.038	30.76 ±0.57
F6	0.3876± 0.025	0.3289± 0.018	12.90 ± 0.011	1.17 ± 0.001	30.73 ±1.83
F7	0.3830± 0.015	0.3262± 0.009	10.32 ± 0.051	1.17± 0.015	33.44 ± 1.28
F8	0.3591± 0.013	0.3284± 0.010	13.52 ± 0.020	1.09± 0.015	27.01 ± 0.45
F9	0.3608± 0.011	0.3270 ± 0.011	14.61 ± 0.030	1.11 ± 0.025	28.84 ±1.01

4.3 Post compression evaluation of Liquisolid tablet of Lercanidipine hydrochloride:

Table 4: Evaluation of Liquisolid tablet

Batch Name	Thickness (mm) ± S.D.	Hardness (kg/Cm^2) ± S.D.	Friability (%) ± S.D.	Uniformity of Weight (mg)	Uniformity of Content (%) ± S.D.	Disintegration time ± S.D.
F1	4.43 ± 0.06	2.74 ± 0.12	0.512 ± 0.07	279.2 ± 1.12	96.95 ± 1.2	7.56 ± 0.18
F2	5.21 ± 0.05	2.47 ± 0.11	0.411 ± 0.02	380.4 ± 0.79	97.26 ± 1.8	7.48 ± 0.28
F3	5.79 ± 0.07	2.87 ± 0.12	0.425 ± 0.01	478.2 ± 1.12	96.05 ± 1.3	7.45 ± 0.18
F4	4.80 ± 0.07	2.83 ± 0.12	0.533 ± 0.02	279.5 ± 0.6	97.60 ± 1.1	7.12 ± 0.08
F5	5.79 ± 0.07	2.75 ± 0.13	0.427 ± 0.05	379.0 ± 0.25	96.20 ± 1.9	8.15 ± 0.21
F6	5.84 ± 0.05	3.12 ± 0.14	0.402 ± 0.01	479.5 ± 0.20	97.47 ± 2.6	7.50 ± 0.19
F7	4.38 ± 0.08	2.72 ± 0.10	0.369 ± 0.01	280.4 ± 0.49	97.50 ± 1.2	7.25 ± 0.22
F8	5.52 ± 0.025	2.91 ± 0.14	0.440 ± 0.02	379.8 ± 0.35	98.56 ± 1.4	6.51 ± 0.15
F9	5.74 ± 0.002	3.10 ± 0.15	0.418 ± 0.02	481.1 ± 1.01	97.17 ± 2.1	8.05 ± 0.05

4.5 FT-IR Spectrum:

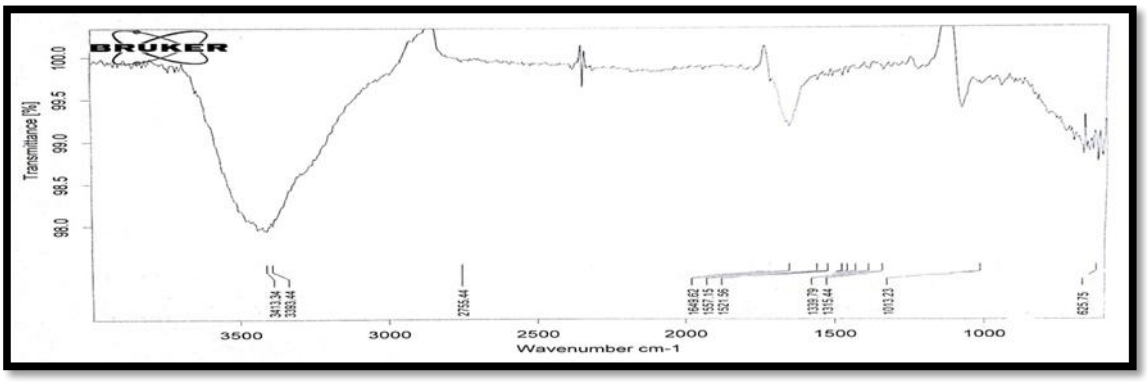

Figure 3:FT-IR spectrum of Lercanidipine HCl

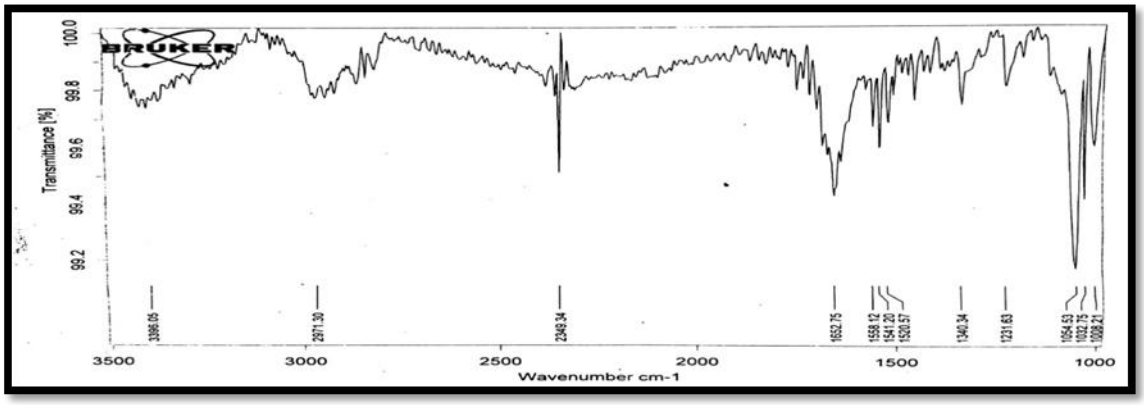

Figure 4: FT-IR spectrum of physical mixture of Lercanidipine HCl with Excipients

FT-IR spectrum of pure Lercanidipine hydrochloride and liquisolid compacts is shown in (Figure-4). 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 liquisolid compacts displayed same characteristic peaks and no possibility of any chemical interaction between the drug and excipients used in the formulation.

4.6 Differential scanning calorimetry (DSC)

DSC thermograph of Lercanidipine is shown in (Figure-6) which shows 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 Lercanidipine hydrochloride liquisolid tablet is shown in (Figure-6) which shows no peak i.e. melting point and amorphous state of drug. This found out that the disappearance of the drug melting peak indicates that amorphization was obtained.

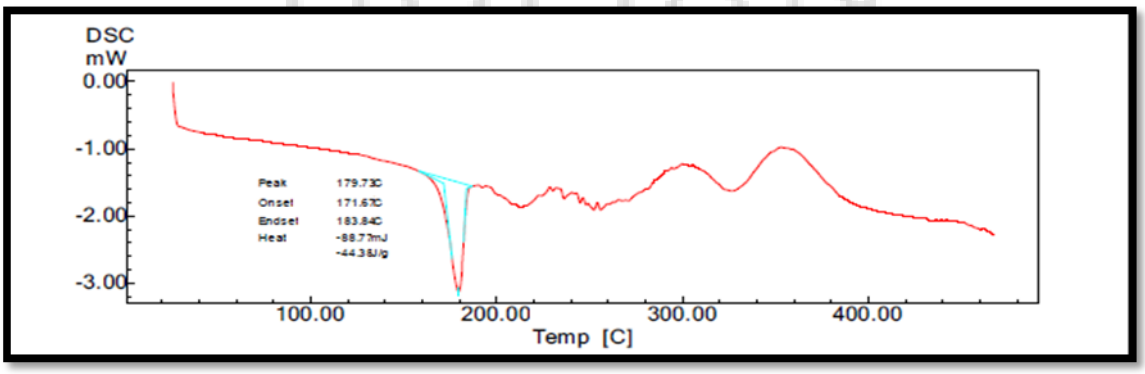

Figure 5: DSC Thermograph of Lercanidipine hydrochloride.

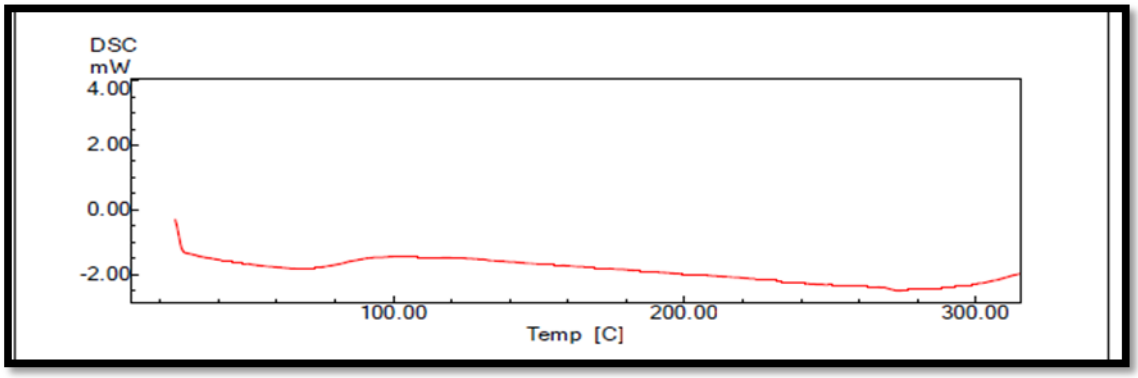

Figure 6: DSC Thermograph of Lercanidipine hydrochloride liquisolid tablet

4.7 X- Ray Diffraction Study:

The Liquisolid system was studied for prediction of crystallinity. The PXRD pattern of Lercanidipine hydrochloride is shown in (Figure 7). Based on the diffractogram it can be suggested that Lercanidipine is present in the crystalline form since it exhibits several well-defined peaks at a diffractogram angle of 2θ. The sharp peaks of carrier are obtained that are shown in figure 8.

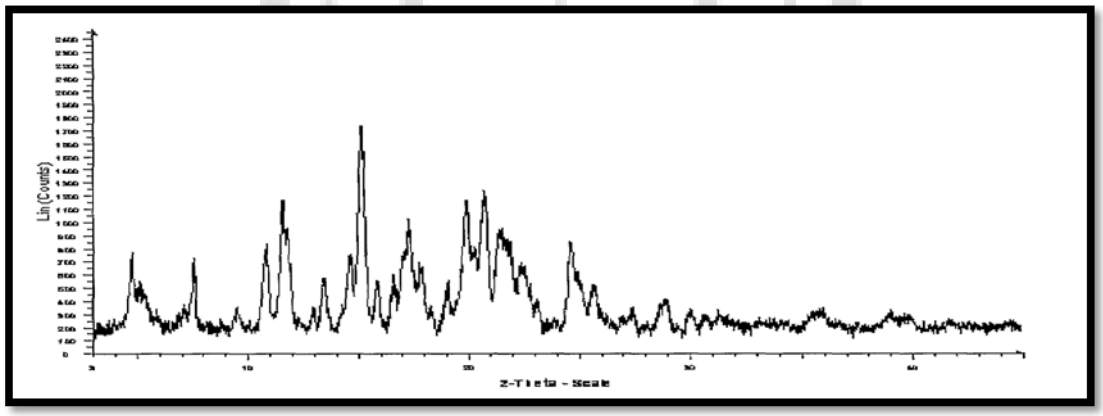

Figure 7: PXRD of Lercanidipine hydrochloride

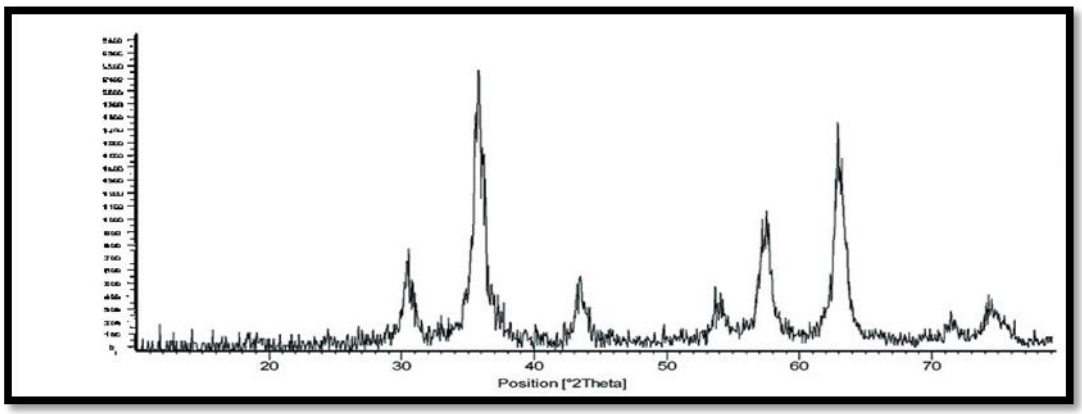

Figure 8: PXRD of Lercanidipine HCl Liquisolid system (Mixture)

4.8 *In- Vitro* release study-

In the dissolution study of Lercanidipine hydrochloride liquisolid tablet the order of improving rate is F8 > F7 > F9 > F4 > F5 > F6 > F2 > F1 > F3. The dissolution profiles of lercanidipine hydrochloride from liquisolid tablets (F1 to F9) produced higher drug dissolution rate in comparison with the conventional tablets. It was apparent that batch F8 formulation has the highest dissolution rate. The percentage of lercanidipine hydrochloride dissolved from F8 reached 82.06 % after 120 min while pure drug show 44.61% and conventional tablet show 54.30% release. It was observed that liquisolid tablet show more solubility than pure drug and conventional tablet.

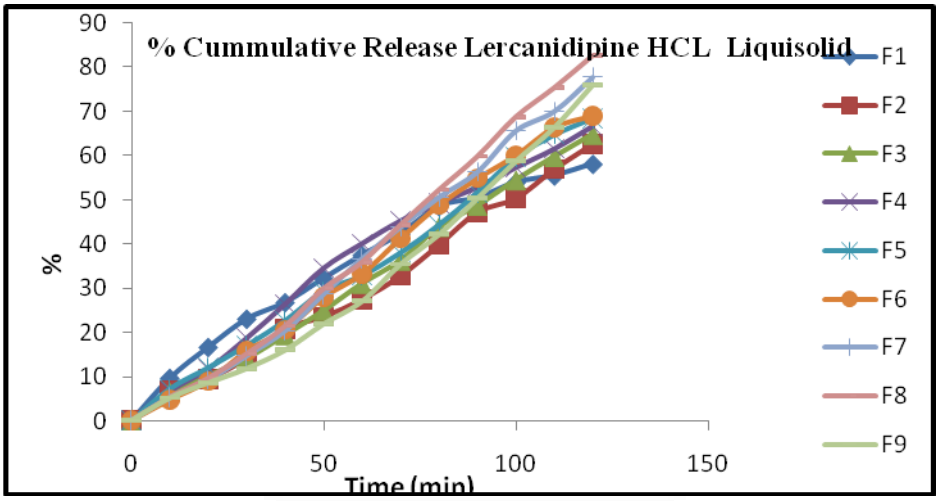

Figure 9: *In-vitro* study of different formulations of Lercanidipine HCl

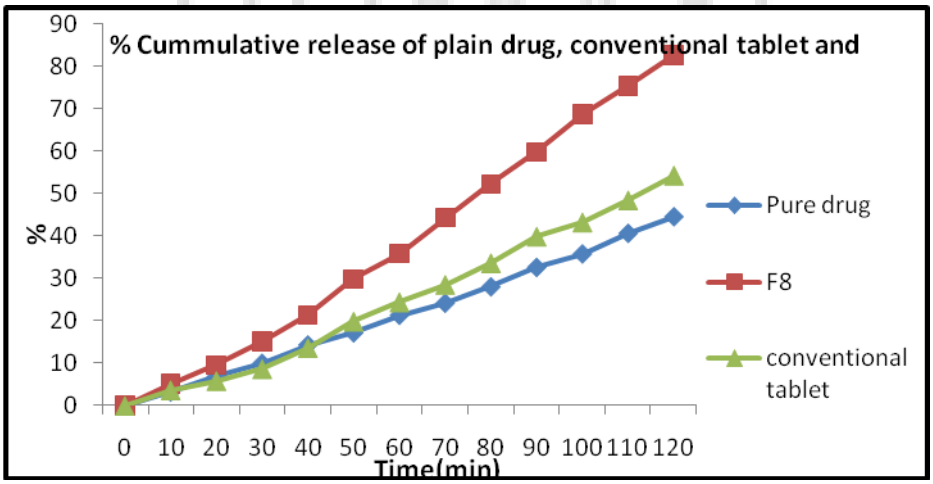

Figure 10: *In-vitro* study of Pure drug, Conventional tablet and (F8) Formulation

5.0 OPTIMIZATION

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The percentage of PEG-400: Avicel-102 (X_1) and Aerosil 200 (X_2) were selected as independent variables and the dependent variable was % CDR after 2 hrs.The data obtained were treated using design expert version 7.1 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the effect of PEG-400: Avicel PH-102 (X_1) and Aerosil-200 (X_2) on dependent variable. Table.5 Shows other statistical parameters for the dependent variable % CDR after 2 hrs. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses.

A) Drug release:

Table 5: ANOVA for % drug release (Y1)

Source	Sum of Squares	Degree of Freedom	Mean Square	F value	P-value	Inference
Model	655.18	2	327.59	53.10	0.0002	Significant
PEG400	17.41	1	17.41	2.82	0.1440	
AVICEL PH-102	637.78	1	637.78	103.38	<0.0001	

Standard deviation = 2.48

R-Squared =0.8684

The Model F-value of 53.10 implies the model is significant. There is only a 0.02% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > P" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. The values of Prob>F were less than 0.05, which indicated model terms were significant. The linear model obtained from the regression analysis used to build a 3-D graph's in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

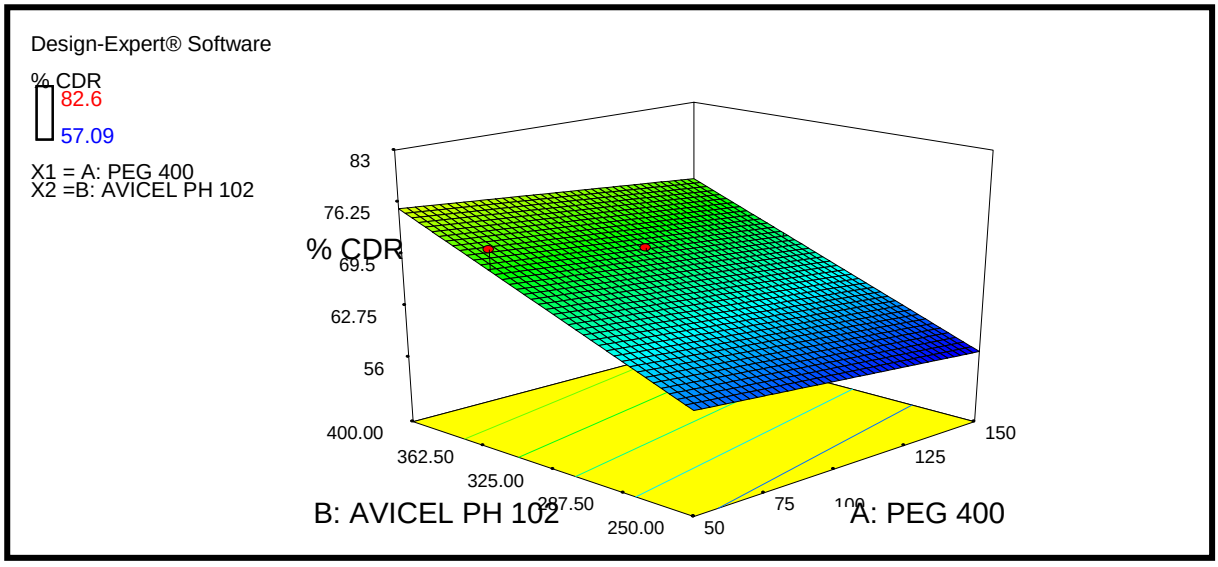

Figure 12: Surface Response plot showing effect of PEG-400 and AVICEL PH-102 on release

B) Contour plot:

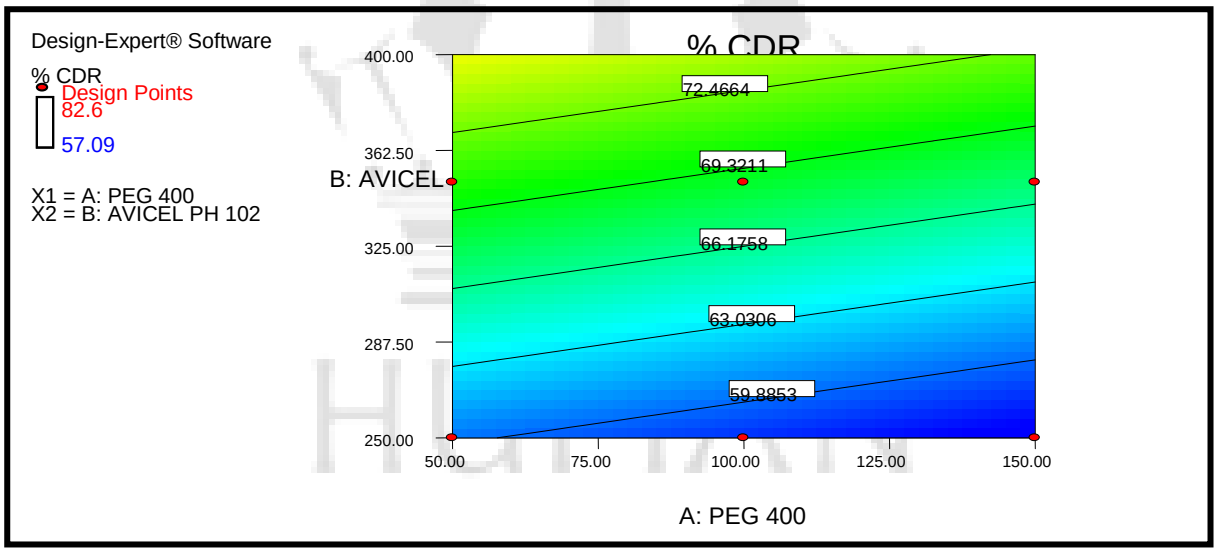

Figure 13: Contour plot showing effect of PEG-400 and AVICEL PH-102 on drug release.

6.0 STABILITY STUDY:

The results of stability study showed that there was no significant change in organoleptic properties, hardness and disintegration. *In vitro* dissolution study of lercanidipine hydrochloride liquisolid tablets. Therefore the results of stability studies showed that formulations have good stability.

7.0 DISCUSSION

In the liquisolid technique the drug is mixed with non-volatile solvent and which is again mixed with carrier and coating material respectively which have specified ratio and finally added super disintegrants. Lercanidipine hydrochloride tablets prepared by liquisolid system. The mechanism of this technique is increasing in solubility, is the wetting of drug particle and increase in surface area of the drug due to that the solubility of drug gets increased. The research shows that the solubility of lercanidipine hydrochloride is practically insoluble water and hence the various non-volatile solvents having more solubility than the water hence among polyethylene glycol, propylene glycol, tween-80, glycerin shows more solubility of lercanidipine, hence polyethylene glycol is selected for the preparation of liquisolid tablets. The microcrystalline cellulose (Avicel PH-102) and Aerosil-200 were selected as carrier and coating material respectively. Then sodium starch glycolate was added as the disintegrant in the formulation. The FT-IR, DSC and X-Ray diffraction studies show no interaction between drug and excipients. In pre-compression study, the all parameters like flow properties- bulk density, tap density, angle of repose, hausner's ratio and carr's index was performed and shows the significant results. In post compression evaluation the diameter, thickness, hardness, weight variation, disintegration time, friability was done. The *in-vitro* evaluation of the lercanidipine liquisolid tablets compared with all bathes the batch having more non-volatile solvent shows fast release of the drug from the tablets such as batch F8 shows fast release of drug than other batches.

8.0 CONCLUSION

Liquisolid technique has long been employed to improve the solubility of drug. Lercanidipine hydrochloride has been selected as model drug because it exhibits pharmacokinetics and physicochemical properties justified for liquisolid technique.Lercanidipine hydrochloride release from Liquisolid tablet is faster than conventional tablet. Lercanidipine hydrochloride particles dispersed the drug particle in non-volatile hydrophilic liquid vehicle, which in turn increase the wetting properties and surface area of drug particle, and improve the solubility hence improve the dissolution rates of formulation (F8). In this study also concluded that investigated liquisolid tablets of lercanidipine with increasing amount of carrier coating ratio with superdisintigrant resulted in higher dissolution rate which is directly proportional to amount of drug release.

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