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SOLUBILITY ENHANCEMENT OF LERCANIDIPINE BY USING SOLID DISPERSION TECHNIQUE AND FORMULATION OF FAST DISSOLVING TABLETS

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KEYWORDS:

Lercanidipine, Solid dispersion, Fast dissolving tablets, *In vitro* dissolution studies.

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ABSTRACT

Lercanidipine (LER) is an oral antihypertensive agent. LER belongs to BCS class II drug having high permeability but low aqueous solubility. The major problem with this drug is its very low solubility in biological fluids, which results in poor bioavailability after oral administration. The solid dispersions of LER with polyethylene glycol 4000 and polyethylene glycol 6000 were prepared by using solvent evaporation method using different ratios with a view to increase its water solubility. The prepared solid dispersion showed improved solubility and dissolution rate as compared to pure drug. FTIR analysis showed no interaction between LER, PEG 4000 and PEG 6000. The solid dispersions with PEG 4000 and PEG 6000 showed maximum drug release. Thus, SD4 and SD8 were incorporated into FDTs containing super-disintegrants (Croscarmellose sodium and sodium starch glycolate). The prepared tablets were evaluated for thickness, hardness, weight variation, friability, drug content, wetting time, water absorption ratio, disintegration time and *in-vitro* drug release. The drug release profile was studied in Phosphate buffer pH 6.8. Among all formulations F8 (containing PEG 6000 SD and Croscarmellose sodium) showed a maximum of 88.62 % drug release in 10 min. F8 was subjected to stability studies. The formulation was found to be stable for two months at 40°C / 75% RH with insignificant change in the physical appearance and drug content.

1. INTRODUCTION:

Lercanidipine hydrochloride chemically is 2[(3,3- diphenylpropyl) (methyl)amino]-1, 1-dimethylethyl methyl 2,6- dimethyl-4- (3-nitrophenyl)-1, 4-dihydropyridine-3, 5- dicarboxylate hydrochloride. It is a novel third generation amphipathic drug belonging to the pharmacological class 1, 4-dihydropyridine calcium channel blockers. Lercanidipine HCl belongs to BSC class II compound and has low aqueous solubility, resulting in low dissolution and poor oral bioavailability. Thus, the improvement of solubility of lercanidipine HCl and in turn dissolution is a critical aspect for improving its bioavailability and therapeutic efficacy. [1-2]

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. When dissolution is rate limited, the buccal delivery of such drug candidates is a tedious task. 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. 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. [3-6]

The objective of this work was to increase the solubility and ultimately dissolution of lercanidipine HCl by dispersing it in the polymer matrix of PEG 4000 and PEG 6000 in different ratios using different techniques. To study the effect of polymer, dissolution and solubility studies were carried out. Solid state characterisations of prepared solid dispersions were performed by differential scanning calorimetry (DSC). Drug carrier interactions were studied by FT-IR spectroscopy, whereas X-ray diffraction of powder was done to demonstrate the crystal structure of the dispersions.

2. MATERIALS AND METHODS

2.1 Materials

Lercanidipine was obtained as gift sample from Torrent Pharmaceuticals Limited, Bhud, Makhnu Majra, Nalagarh, Solan (HP). PEG 4000, PEG 6000, Talc, Magnesium Sterate was obtained from SD Fine Chemicals, Mumbai. The Croscarmellose sodium, Sodium starch glycolate, microcrystalline cellulose was obtained from DFE Pharma, Banglore.

2.2 Formulation of Solid Dispersion (SD)

The SD was prepared by melting fusion method. Weighed amount of drug was melted with PEG 4000 and PEG 6000 polymer at 60°C. Then melted polymer and drug were stirred and immediately cooled in

an ice bath and obtained solidified mass was crushed in mortar pestle and passed through sieve. The obtained solid dispersion was stored in the desiccators until used for further evaluation. [7]

Table 1: Formulation batches of Lercanidipine solid dispersion

Formulations	Ratio	Drug + Polymer
SD1	**1:1**	Lercanidipine + PEG 4000
SD2	**1:2**	
SD3	**1:3**	
SD4	**1:4**	
SD5	**1:1**	Lercanidipine + PEG 6000
SD6	**1:2**	
SD7	**1:3**	
SD8	**1:4**	

2.3 Evaluation of Solid Dispersion

2.3.1 Percentage yield

Thoroughly dried solid dispersion was collected and weighed accurately. The percentage yield was then calculated by using Eq.1.

$$\text{Percentage yield} = \frac{\text{Mass of solid dispersion}}{\text{Total weight of drug and polymer}} \times 100 \quad \text{.....Eq.1}$$

2.3.2 Estimation of drug content

Weighed quantity of SD equivalent to 10 mg of drug was added in 100 ml volumetric flask containing 5 ml of methanol. The material was mixed properly. The final volume was made up to 100 ml with phosphate buffer pH 6.8 and was spectrophotometrically analyzed at 241 nm. [8]

2.3.3 Fourier Transform Infrared Spectroscopy (FTIR)

The interference study was carried out using FTIR analysis. IR spectrum of pure drug and mixture of drug- polymer i.e. PEG 4000 and PEG 6000 was performed for polymer drug interaction studies between 4000-400 cm-1 using KBr pellet method.

2.3.4 *In vitro* release studies of solid dispersion and pure drug (Lercanidipine)

The *in vitro* dissolution study was carried out in the USP dissolution apparatus type 2 (paddle) 900 ml of phosphate buffer pH 6.8 maintained at 37±0.5^{o}C was taken as the dissolution medium. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn at selected time intervals (15, 30, 45, 60, 75, 90 min) and the same amount was replaced with the fresh medium. The withdrawn sample was filtered and analyzed by using UV spectrophotometer at 241 nm. The mean ± SD (standard deviation) values were calculated. [9]

2.4 Preparation of Fast Dissolving tablets (FDTs) containing Solid Dispersion by Direct Compression method

The SD formulation which showed maximum dissolution rate was selected to formulate FDTs. The SD equivalent to 10 mg of Lercanidipine was taken. Then it was mixed with directly compressible diluents and superdisintegrants in the mortar pestle. Magnesium stearate and talc were passed through sieve no. 60 and mixed with the initial mixture in the mortar pestle followed by compression of the blend. [10] The formulation composition is shown in table 2.

Table 2: Formulation chart of FDTs containing solid dispersion

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
SD with PEG 4000 (1:4)	25	25	25	25	-	-	-	-
SD with PEG 6000 (1:4)	-	-	-	-	25	25	25	25
Sodium starch glycolate	3	5	-	-	3	5	-	-
Croscarmellose sodium	-	-	3	5	-	-	3	5
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Microcrysttaline Cellulose	68	66	68	66	68	66	68	66
Net weight (mg)	100	100	100	100	100	100	100	100

2.5 Evaluation of FDTs containing Lercanidipine SD

Evaluation of Pre-compression Parameters

The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The results obtained are mentioned in table 4.

2.5.1 Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle of repose (θ) was determined by using funnel method. The blend was poured through a funnel. The funnel

was raised vertically until a maximum cone height (h) was obtained. [11] The radius of the heap was measured and angle of repose was calculated by using Eq.2.

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

$$\theta = \tan^{-1} (h/r) \quad \text{.....Eq.2}$$

where, θ = angle of repose of the blend, h = the height of heap and r = the radius of heap

Table 3: Angle of repose and quality of the flow

S.No	Angle of Repose	Quality of flow
1.	<25	Excellent
2.	25-30	Good
3.	30-35	Passable
4.	>40	Very poor

2.5.2 Bulk density and tapped density

The bulk density of powder was obtained by dividing its mass by the bulk volume. It is expressed in g/cc. 10 g of the granules (W) were weighed and poured through funnel into a 100 ml measuring cylinder. The initial volume occupied by the sample was recorded. The cylinder was then allowed to fall under (tapped) its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. [12] The bulk density and tapped density were calculated by using Eq.3 and Eq.4 and mean ± SD (standard deviation) values were calculated.

$$\text{Bulk density} = W/Vo \quad \text{.....Eq.3}$$

$$\text{Tapped density} = W/V_F \quad \text{.....Eq.4}$$

Where, W = weight of granules, V_0= initial volume of the granules and V_F = final volume of the granules.

2.5.3 Compressibility index (Carr's index)

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which material can be induced to flow is given by % compressibility which is calculated by using Eq.5 and mean ± SD (standard deviation) values were calculated.[13]

$$C = (\rho t - \rho b) / \rho t \times 100 \quad \text{.....Eq.5}$$

Where, ρt is tapped density and ρb is untapped density.

2.5.4 Hausner's ratio

Hausner's ratio is an index of ease of powder flow. [13] It is calculated by using Eq.6 and mean ± SD (standard deviation) values were calculated.

Hausner'sratio = ρt /ρb……..…..……..Eq.6

Where, ρt = Tapped density, ρb = Untapped density.

2.6 EVALUATION OF FDTs

The prepared tablets were evaluated for post - compression parameters like weight variation, hardness, % friability, disintegration time, wetting time, dispersion time, drug content and dissolution studies.[14-15]

2.6.1 Weight variation

20 tablets were selected at a random from each formulation and average weight was determined. Then individual tablets were weighed and compared with the average weight. The % weight variation of each individual tablet from the average weight is calculated by using Eq.7 given below.

$$\%\text{Weight Variation} = \frac{\text{Individual weight of each tablet} - \text{Average weight of 20 tablets}}{\text{Average weight of 20 tablets}} \times 100 \quad \text{Eq.7}$$

2.6.2 Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance. The thickness of tablet was determined by using screw gauge and mean ± SD (standard deviation) values were calculated.

2.6.3 Hardness

Harness indicates the ability of a tablet to withstand mechanical shocks while handling. Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean ± SD (standard deviation) values were calculated.

2.6.4 Friability

Friability of tablets was determined by using Roche Friabilator. This device subjects the tablets to combined effects of abrasions and shock in a plastic chamber at 25 rpm and dropping the tablets at a distance of 6 inches with each revolution. Ten pre-weighed tablets were placed in chamber and subjected to 100 revolutions for 4 minutes. After these revolutions tablets were dedusted using a soft muslin cloth and reweighed. The friability was calculated by using Eq.8.

$$F = (W_0 - W) / W_0 \times 100 \quad \text{Eq.8}$$

Where, W_0 is the weight of tablets before test, W is the weight of the tablet after the test. Tablets are of good quality if loss on weight is less than 1%.

2.6.5 Wetting time and Water absorption ratio

Wetting time of the FDTs is another parameter, which needs to be assessed to give an insight into disintegration properties of the tablet. It corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. Lower wetting time implies a quicker disintegration of the tablet. A piece of tissue paper folded double was placed in a Petri plate (internal diameter 6.5 cm) containing 6ml

of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For measuring water absorption ratio, the weight of the tablet before keeping in a petri dish was noted (w_b). The wetted tablet from the petri dish was taken and reweighed (w_a). The water absorption ratio, R can be determined by using Eq.9.

$$R = 100 (W_a – W_b) / W_b \text{……..Eq.9}$$

Where, $W_a$is weight of wetted tablets and W_b weight of tablets before wetting.

2.6.6 *In vitro* dispersion time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 50 ml Phosphate buffer pH 6.8. The time required for complete dispersion of tablets was measured and the mean ± SD (standard deviation) values were calculated.

2.6.7 % drug content determination

Five tablets were crushed in a glass mortar pestle. Then weight of powder equivalent to 10 mg Lercanidipine was taken and dissolved in 100 ml of Phosphate buffer pH 6.8 in the volumetric flask. The flask was shaken for 4 h in a mechanical shaker. The solution was filtered through whatmann's filter paper and analyzed at 241 nm using a UV-visible double beam spectrophotometer. Each sample was analyzed in triplicate.

2.6.8 *In vitro* disintegration time

Disintegration time of prepared tablets was determined in disintegration test apparatus. It consist of 6 glass tubes which are 3 inches long open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test the disintegration time of tablets, One tablet from each formulation was placed in each tube and the basket rack was positioned in a 1 litre beaker containing phosphate buffer pH 6.8 maintained at a temperature 37± 2°C. The tablet should remain 2.5 cm below the surface of the liquid. The time taken for complete disintegration of the tablets with no particulate matter was noted and the mean ± SD (standard deviation) values were calculated.

2.6.9 *In vitro* Drug dissolution studies

The dissolution profile of FDTs of lercanidipine was carried out in a beaker containing 30 ml of Phosphate buffer pH 6.8 as a dissolution medium, maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 min time intervals and the same amount was replaced with the fresh medium. Samples were analyzed by using UV spectrophotometer at 241 nm. Each test was carried out in triplicate. The percentage of the drug dissolved at various time intervals was calculated and plotted against time. [16]

2.7 STABILITY STUDY

The purpose of stability testing is to provide evidence on how the quality of a drug substance of the drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light to establish a re – test period for the drug substance or a shelf life for the drug product and recommended storage conditions. The stability study was carried out at 40^0C / 75% RH for two month. The tablets were wrapped in the aluminium foil and stored in a stability chamber at accelerated conditions. [17] The drug content was checked at regular time intervals of 15, 30, 45 and 60 days respectively and was evaluated for physical appearance.

3. RESULTS AND DISCUSSION

3.1 Evaluation of Solid Dispersions

3.1.1 Percentage Yield

The yield obtained was in the range of 89.04% to 95.14%. The maximum percentage yield was obtained in SD4 and SD8 with 94.25% and 95.14% respectively.

3.1.2 Estimation of drug content

The drug content obtained was in the range of 96.11±0.09 to 99.62±0.07%. Maximum drug content was obtained in SD4 and SD8 solid dispersion with 98.34±0.12% and 99.62±0.07% respectively.

3.1.3 Fourier Transform Infrared Spectroscopy (FTIR) It was observed that there is no interaction between drug and polymers shown in figure 1, 2 and 3.

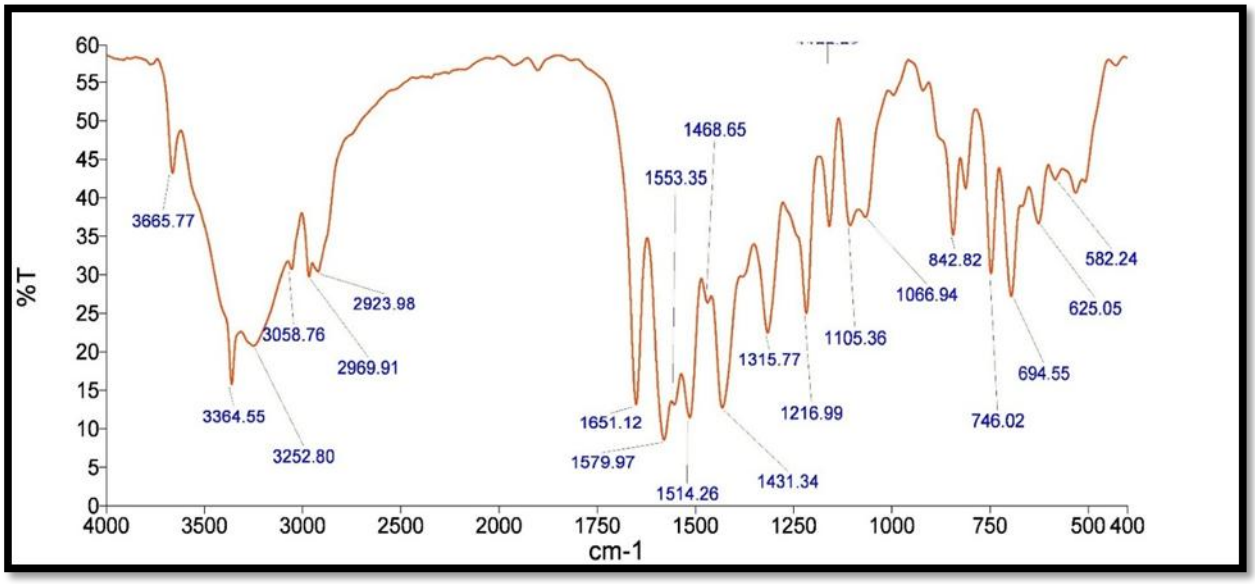

Figure 1: FTIR of Lercanidipine

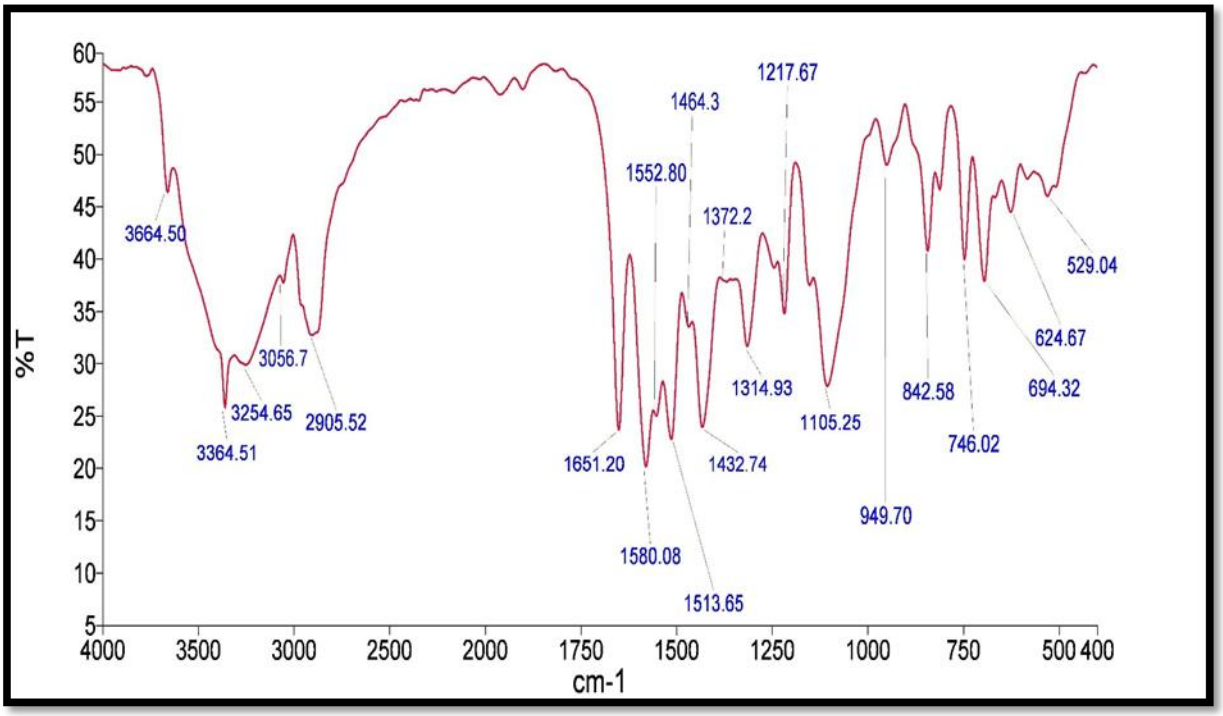

Figure 2: FTIR of Lercanidipine with PEG 4000

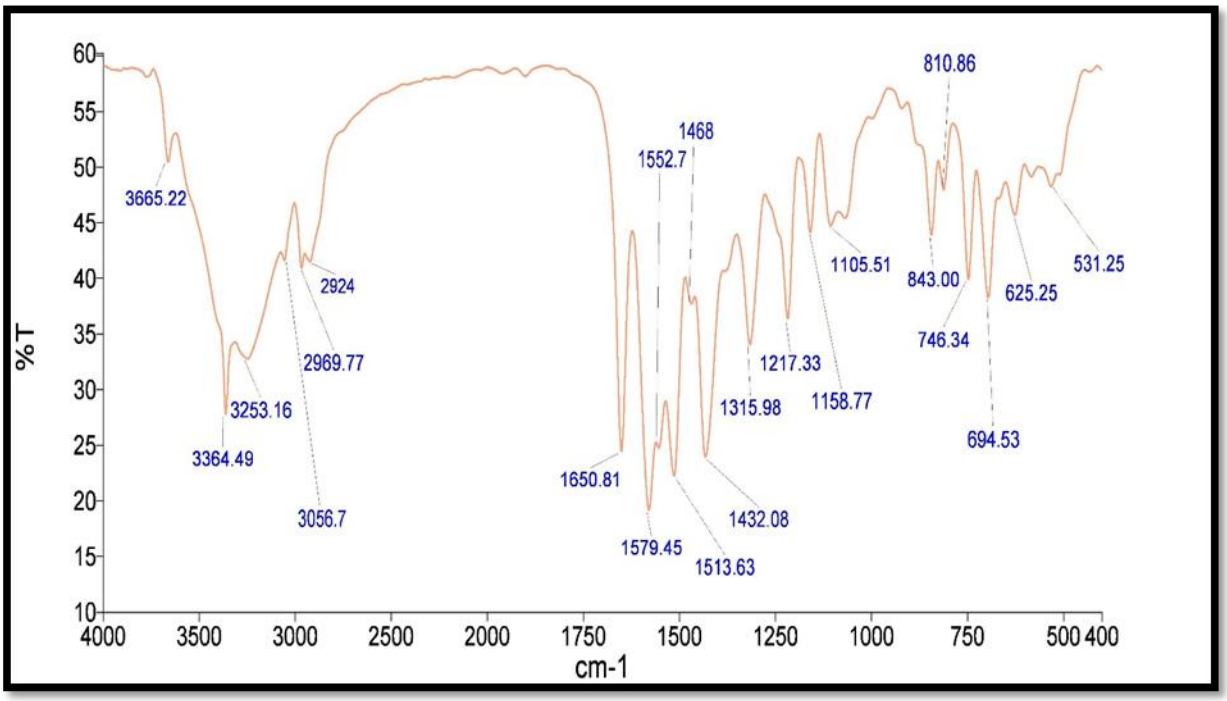

Figure 3: FTIR of Lercanidipine with PEG 6000

3.1.4 *In vitro* release studies of solid dispersion and pure drug (Lercanidipine)

From the data, it was observed that maximum amount of drug released was obtained in SD4 and SD8 solid dispersion with 75.43% and 83.22% respectively in 90 min, whereas the pure drug released

maximum 21.68% of drug in 90 min. The graph is shown in figure 4. Hence, formulations SD4 and SD8 were selected for further formulation study of Fast Dissolving Tablets.

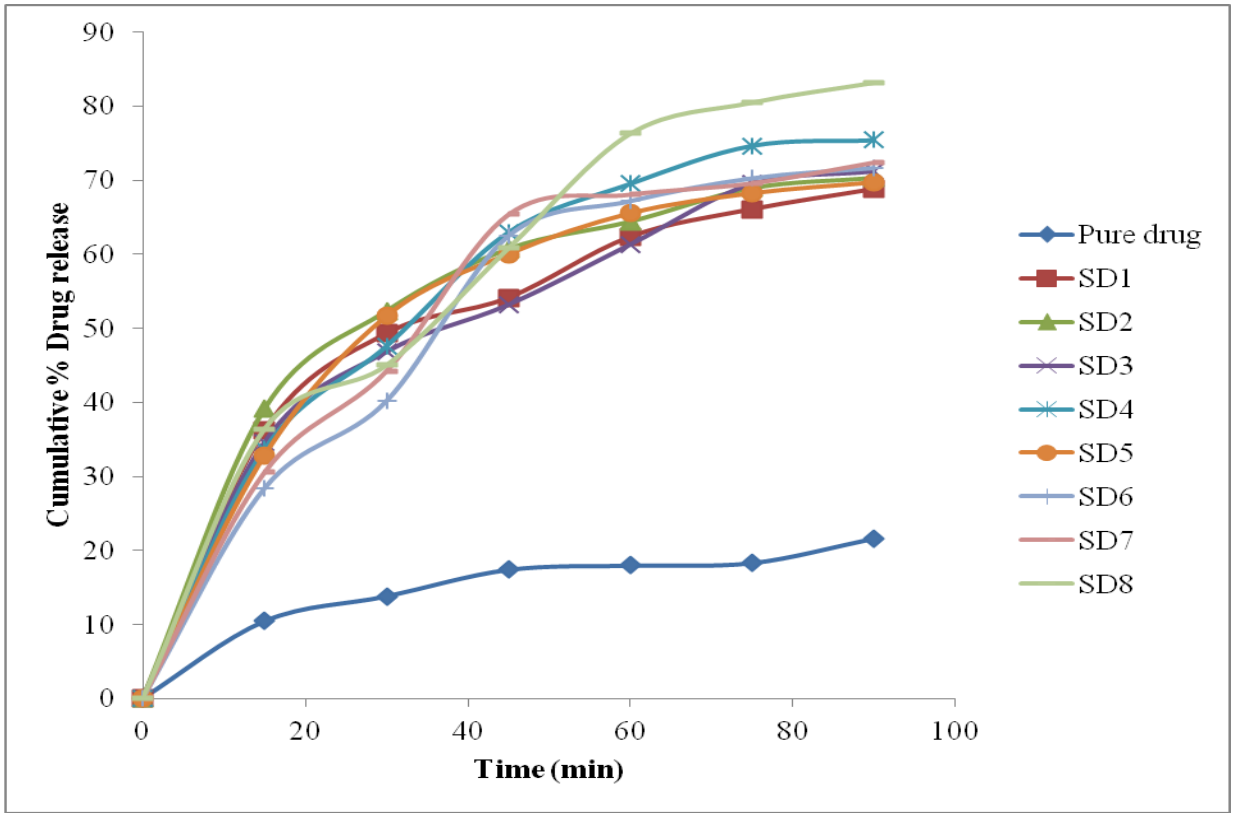

Figure 4: Cumulative % Drug Release of Lercanidipine pure drug and SDs

3.2 Evaluation of FDTs containing Lercanidipine SDs

Table 4: Data of Pre-compression parameters

Formulation code	Angle of Repose (θ) ±SD	Bulk Density (g/cc) ± SD	Tapped density (g/cc) ± SD	Carr's Index (%) ± SD	Hausner's Ratio ±SD
F1	22.18±1.20	0.42±0.01	0.57±0.02	14.5±1.05	1.16±0.02
F2	23.74±0.04	0.51±0.03	0.59±0.03	16.5±0.98	1.14±0.01
F3	23.14±0.01	0.53±0.02	0.65±0.01	20.1±0.61	1.17±0.03
F4	21.47±0.51	0.52±0.01	0.62±0.04	12.3±0.02	1.14±0.05
F5	22.47±0.76	0.48±0.06	0.54±0.01	15.7±1.32	1.18±0.08
F6	23.64±1.28	0.46±0.03	0.67±0.01	13.4±1.79	1.10±0.06
F7	22.81±0.68	0.41±0.02	0.56±0.02	18.9±1.81	1.15±0.04
F8	24.85±0.32	0.45±0.04	0.58±0.03	17.8±0.01	1.17±0.02

***All readings are in triplicate (n=3) and SD= Standard Deviation

Table 5: Observations of different post-compression of FDTs

Formulation Code	Weight Variation test (mg) ±SD	Thickness (mm) ±SD	Hardness (Kg/cm^2) ±SD	Friability (%) ±SD
F1	99.28±0.19	3.15±0.04	2.8±0.04	0.56±0.06
F2	99.65±1.08	2.83±0.07	2.6±0.07	0.67±0.07
F3	99.05±1.83	3.05±0.12	3.0±0.02	0.78±0.05
F4	98.77±0.49	3.16±0.05	2.7±0.18	0.59±0.03
F5	99.37±1.30	3.20±0.18	2.8±0.05	0.72±0.04
F6	99.48±0.76	3.07±0.11	2.6±0.12	0.80±0.06
F7	99.16±0.91	2.98±0.08	2.9±0.04	0.63±0.08
F8	98.92±0.96	3.12±0.09	2.7±0.15	0.75±0.05

*All readings are in triplicate (n=3) and SD= Standard Deviation

Table 6: Observation of evaluation parameters of FDTs

Formulation Code	Wetting time (sec) ±SD	Water absorption ratio (%) ±SD	*In vitro* dispersion time (sec) ±SD	Disintegration Time (sec) ±SD	% Drug Content (%) ±SD
F1	32±0.58	76.35±1.25	24±0.14	47±0.62	98.02±0.12
F2	29±0.75	72.12±1.31	23±0.16	38±0.85	99.26±0.37
F3	37±0.63	84.28±0.47	28±0.05	35±0.49	98.72±0.28
F4	26±0.86	81.13±0.18	21±0.12	49±1.67	99.32±0.02
F5	39±0.92	68.32±0.50	22±0.11	32±0.68	99.41±0.11
F6	35±0.52	75.21±0.45	23±0.15	30±1.23	98.35±0.16
F7	44±0.78	92.74±0.68	25±0.08	52±1.02	98.52±0.18
F8	41±0.96	88.27±0.28	22±0.02	44±0.72	98.53±0.01

*All readings were in triplicate (n=3) and SD=Standard Deviation

3.2.1 *In vitro* Dissolution study of FDTs

The formulation F4 (PEG 4000) released 79.46% of drug whereas the formulation F8 (PEG 6000) released 88.62% of drug in 10 min. On the basis of drug release, formulation F8 containing crosscarmellose sodium as superdisintegrant released drug at a faster rate. Therefore, formulation F8 was selected as the best formulation. In vitro drug release study data is shown in table 5.6 and graph between cumulative % drug release versus time is shown in figure 5.2.

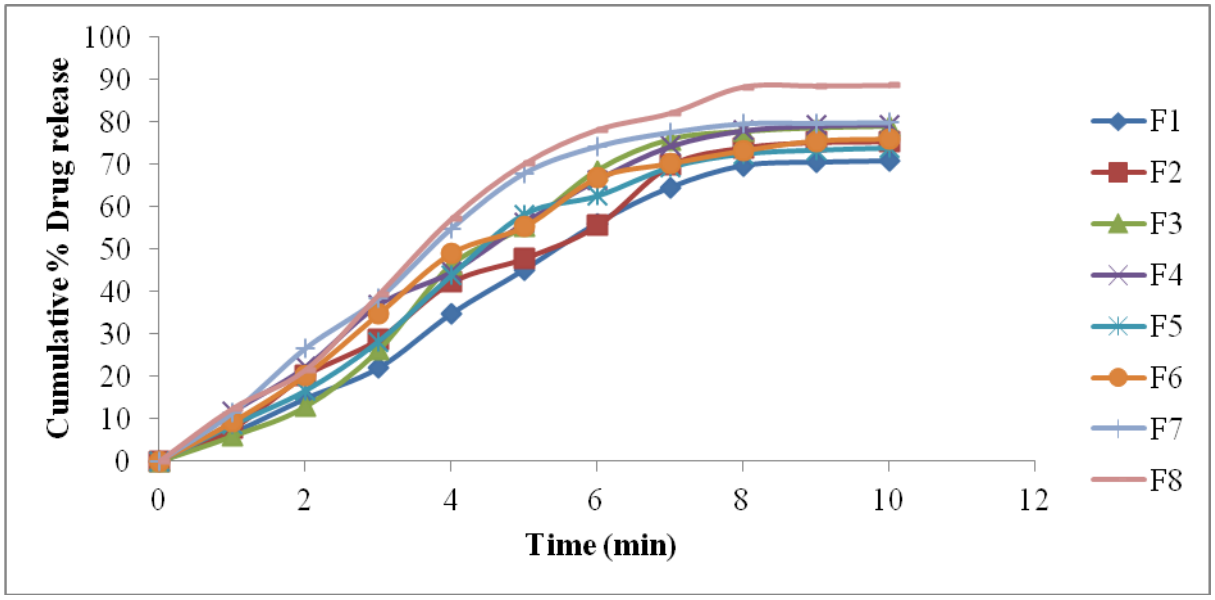

Figure 5: Cumulative % Drug Release of Lercanidipine pure drug and SD_8

3.3 Stability study of formulation (F8)

The stability study of formulation (F8) was carried out at 40^0C / 75% RH for two month. The tablets were wrapped in the aluminium foil and stored in a stability chamber at accelerated conditions. The drug content was checked at regular time intervals of 15, 30, 45 and 60 days respectively and was evaluated for physical appearance. The results of drug content are shown in table 7. There was no significant change in physical appearance, Drug content at the end of two months.

Table 7: Drug Content data during Stability Study

Time (days)	Accelerated conditions (40± 2^0C / 75 ± 5% RH)	
	Physical Appearance	Drug Content
0	+	99.53±0.38
15	+	99.38±0.17
30	+	99.13±0.06
45	+	98.82±0.11

60	+	98.29±0.05

(+) indicates no change in physical appearance

CONCLUSION

In the present research work, an attempt was made to formulate fast dissolving tablets of Lercanidipine (LER). As LER is a BCS Class II drug with low solubility and high permeability. Therefore, the solid dispersions were prepared to improve the solubility of the drug. They were prepared by solvent evaporation method using two different polymers i.e. PEG 4000 and PEG 6000. On the basis of dissolution studies SD4 and SD8 solid dispersions were selected for tableting. Eight formulations of fast dissolving tablets were prepared. All the formulations F1 to F8 were subjected to *in vitro* release studies and formulation F8 showed maximum release 88.62% of drug in 10 min.

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