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DEVELOPMENT AND EVALUATION OF LERCANIDIPINE FAST DISSOLVING TABLETS USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

The objective of the present study is to formulate the fast dissolving tablet of lercanidipine they are use the various Superdisintegrants over commonly used in Different Concentrations. The Super disintegrants are Crospovidone, Croscarmellose use, Sodium Starch glycolate. Lercanidipine is a dihydropyridines derivative. Lercanidipine is a calcium antagonist of the dihydropyridines 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. Formulations containing Lercanidipine, Polxmer 188, Aerosil (300) solid dispersionsin 1:4:2 ratio prepared by Hot melt technique showed better Drug content dissolution rate. The disintegration time of optimized formulation F3 was found to 17±0.18 seconds. It was found that as the concentration of Superdisintegrants was increased, the time taken for wetting was reduced. The wetting time of F3 formulation was found to be 38±0.11 seconds. In-vitro disintegration of batch F3 gives rapid disintegration time and wetting time. Drug content was found to be 99.11% Results of in-vitro dissolution data shows that from formulation F1-F9 the batch F3 gives the drug release up to 98.03% in 25 min. Hence formulation F3 subjected for stability studies. Optimum formulation F3 is stable under stability conditions.

KEYWORDS: Lercanidipine HCL, Fast Dissolving Tablet, In –vitro disintegration time.

INTRODUCTION

There is general consensus in the pharmaceutical industry that poorly water-soluble drug candidates are becoming more prevalent.[1,2] Formulation plays a major role in determining the rate and extent of absorption of such drugs from the gastrointestinal tract. When water-

solubility is less than 1_g/ml, which is often the case for contemporary drug candidates, the bioavailability from conventional tablet formulations may be unacceptable. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability.[3,4] Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs.[5,6,7] The choice of formulation is often of critical importance to establishing a successful product for oral administration of a class II drug. If bioavailability of the drug is recognized to be formulation-dependent at an early stage it is desirable to have a strategy for maximizing absorption as soon as possible.[8]

The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method or fusion solvent method. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[9] One of the most promising methods for promoting the dissolution of poorly water-soluble drugs is solid dispersion method. However, the difficulty of pulverization, poor compressibility and poor flow of SDs prepared with water-soluble polymers are challenging factors. These properties have led to a decrease in the usefulness of SDs and handling difficulties in the manufacturing process. SD via an efficient carrier A free-flowing SD granule was prepared by adsorbing the melt of the drug and poloxamer 188 onto the surface of an adsorbent.[10] For drugs that have very poor aqueous solubility, the rate at which the drug dissolves(dissolution)is often the lowest step and there for exhibit eliminating effect on drug bioavailability. Fast dissolving tablet sare those when put on tongue disintegrate instantaneously releasing the drug which dissolve orodispersesion the saliva.[11]

Lercanidipine is a new Calcium channel blocker and antihypertensive drug is class of dihydropyridines. Lercanidipine is completely absorbed after oral administration. Peak plasma levels of 3.30 ng/mL±2.09 s.d and 7.66 mg/mL±5.90 s.d occur 1.5-3 hours after dosing with 10 mg and 20 mg, respectively. The absolute bioavailability of lercanidipine is about 10%, because of high first pass metabolism.[12]

MATERIALS AND METHOD

Materials

Lercandipine Was Obtain as gift sample from Glenmark Pharmaceutical Ltd, Mumbai. India Lutrol F68 was obtained as obtained as gift sample from the BASF (Mumbai, India).

Crospovidone, Croscarmellose Sodium Starch Glycolate was purchased from the Yarrow chem, Mumbai. Talc, Aerosil, Microcrystalline cellulose obtained from Signet chemicals, Mumbai. Indiaand Magnesium stearate, were obtained from S.D. Fine chemicals Pvt. limited, Mumbai. All the chemicals and solutions used were of analytical grade.

Method

Preparation of solid dispersion[10]

The solid dispersion (SD) granules of Lercanidipine were prepared using a hot melt method. The poloxamer 188 carrier was melted in a beaker at 60 ◦C in an oil bath and the drug was added while stirring to obtain a homogenous mixture. Adsorbent (Aerosil 300) were added gradually to the molten mixture with continuous stirring. The dispersion was cooled at followed by passing through a sieve 100 um in diameter. The weight ratio of Lercanidipine, poloxamer 188 and adsorbent is mention in Table 1.

Table 1: Formulation Codes of Solid Dispersion.

Batch Code	Solid Dispersion	Method
A1	Drug : Polxmer 188:Aersil (1:1:1)	Hot melt method
A2	Drug : Polxmer 188:Aerosil (1:2:1)	Hot melt method
A3	Drug : Polxmer 188:Aerosil (1:4:2)	Hot melt method
A4	Drug : Polxmer 188:Aerosil (1:6:3)	Hot melt method

Drug Content Study of Solid Dispersion

Drug content was determined by dissolving solid dispersion equivalent to 10 mg of drug in the 0.1 N HCl and adjusted the volume up to 100ml. the solution was filtered through the whatman paper no 41, suitably diluted and absorbance was measured at 238 nm using the UV spectrophotometer (Shimadzu 1700, Japan).

Differential Sacnning Calorimetry

Differential Scanning Calorimetry(DSC) was performed using Schimazdu DSC 60 instrument. The samples were hermatically sealed in aluminium pans and heated over the temperature range 35° C to 300° C with heating rate of 10℃/min. Inert atmosphere was provided by urging nitrogen gas flowing at 10 ml/min.

X-ray Diffraction Study

The powder X-ray diffraction pattern was determined for lercanidipine and lercanidipine: Solid Dispersion. X-ray diffract gram were obtained using x-ray diffractometer. Philip

diffractometer (PW1140) and Cu-k radiation diffrctogram were run at a scanning speed of 2^0/ mm and a chart speed of 2^0/mm per 2θ.

Dissolution Studies of SD Granules

Dissolution studies of pure drug, and SDs granules, were performed by using the USP dissolution test apparatus-2 at the paddle rotation speed of 50 rpm in 900 mL 6.8 phosphate buffer as dissolution medium at 37±0.5°C. The SDs granules or pure drug equivalent to 10 mg of lercanidipine were weighed and added into the dissolution medium. At the specified times (every 5 min to 60 min), 5 mL samples were withdrawn and then analyzed for Lercanidipine content by measuring the absorbance at 238 nm using a UV-Visible spectrophotometer (Shimadzu UV-1700, Japan). Fresh medium (5mL), which was pre warmed at 37 °C, was added to the dissolution medium after each sampling to maintain its constant volume throughout the test.

Preparation of Fast Dissolving tablets[13]

The best solid dispersion best solid equivalent to10mg of drug were taken then mixed with directly compressible diluents and Superdisintegrants, Magnesium Stearate and talc were passed through sieveno.100, mixedandblended with initial mixture followed by compression end. The compositions of the different formulations are given in the Table 2.

Table 2: Formulation Code of Fast Dissolving Tablet.

Ingredients (Mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid Dispersion equivalent to 10 mg of lercanidipine	70	70	70	70	70	70	70	70	70
Crospovidone	4	6	8	-	-	-	-	-	-
Croscarmellose	-	-	-	4	6	8	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	4	6	8
MCC (Avicel PH-102)	50	50	50	50	50	50	50	50	50
D-Manntiol	23	21	19	23	21	19	23	21	19
Magnesium Stearate	1	1	1	1	1	1	1	15	15
Talc	1	1	1	1	1	1	1	1	1
Aspartam	1	1	1	1	1	1	1	1	1
Total	150	150	150	150	150	150	150	150	150

Evaluation of SD granules Fast Dissolving Tablets

Thickness

Thickness and diameter were measured using a vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Friability

For friability 20 tablets from each batch were examined using Roche friabilator and the equipment was run for 4 min at 25 revolutions per minute. The tablets were removed from friabilator, dedusted the tablet and reweighed. The percent friability was calculated as loss in weight.

Percentage Friability (%) = $\frac{\text{Initialweight} - \text{Finalweight}}{\text{Initialweight}}$ X 100

Weight variation[14]

Weight variation test was conducted by selecting 20 tablets at random. Weighed each tablet on electronic balance and calculated the average weight of tablet. It is the individual variation of tablet weight from the average weight of 20 tablets.

Drug content

Twenty tablets from each batch were powdered and accurately weighed (10 mg) and dissolved in methanol; solution was then suitably diluted with methanol in 100 ml volumetric flask to get final stock solution of concentration 100µg/ml. Accurately pipette out 0.2, 0.4 and 0.6 ml of the above solution into three 10 ml standard flasks and the volumes were made using methanol. The sample solution having concentration 2, 4 and 6 µg/ml. The absorbance of each concentration was measured at 238 nm and calculated the drug content.

Wetting time

A piece of tissue paper (10.75×12 mm) folded twice was placed in a petridish (d=6.5 cm) containing 6 ml of water. A tablet was put on the paper and the time required. All parameter are shown in Table No 3.

Table 3: Evaluation of various parameters of tablets (n=3).

Formulation Code	Thickness (mm)	Wetting Time	Friability (%)	Drug content (%)	Disintegration time
F1	3.2±0.11	57±0.6	0.43± 0.18	98.47 ± 0.40	29±0.21
F2	3.1±0.15	49±0.20	0.60± 0.07	98.12 ± 0.41	21±0.21
F3	3.3±0.05	38±0.11	0.47 ± 0.03	99.11 ± 0.50	17±0.18
F4	3.2±0.10	47±0.12	0.58 ± 0.01	98.12 ± 0.65	38±0.35
F5	3.0±0.20	61±0.33	0.60± 0.11	98.14 ± 0.35	29±0.28
F6	3.1±0.03	55±0.26	0.61± 0.02	99.05 ± 0.55	21±0.20
F7	3.2±0.15	54±0.12	0.42± 0.18	100.74 ±0.40	36±0.25
F8	3.1±0.12	49±0.14	0.50± 0.10	98.43 ± 0.45	31±0.22
F9	3.2±0.03	51±0.15	0.55± 0.01	98.43 ± 0.45	24±0.22

In-vitro dissolution studies

Dissolution study was conducted for all the formulations using USPXXVIII test apparatus 2 (paddle type) (Electro lab TDT-08L). Dissolution test was carried out using 900 ml of phosphate buffer (pH 6.8), at 37^{o}C ± 0.5^{o}C for 25 min at 50 rpm. A sample (5 ml) of the solution was withdrawn from dissolution apparatus at 5, 10, 15, 20, 25 min. and withdrawn volume of sample replaced with fresh dissolution media. The samples were filtered through whatman filter paper and analyzed the samples by UV Spectrophotometry (Shimadzu 1700) at 238 nm.

Zero-order, first-order, Higuchi and Korsmeyer–Peppas kinetic models were performed to study the drug release kinetic. As shown in table no 4.

Table 4: Kinetic Modeling of Different Batches (F1-F9).

Formulation Code	Zero Order equation R^2	First order equation	Higuchi equation	Korsmeyer-Peppas equation	
		R^2	R^2	R^2	n
F1	0.834	0.961	0.836	0.836	1.2512
F2	0.907	0.931	0.823	0.817	1.2662
F3	0.828	0.969	0.983	0.783	1.2494
F4	0.925	0.943	0.782	0.840	1.2525
F5	0.867	0.946	0.947	0.805	1.2712
F6	0.833	0.949	0.956	0.845	1.2558
F7	0.934	0.944	0.963	0.835	1.2629
F8	0.951	0.933	0.924	0.823	1.2449
F9	0.983	0.905	0.992	0.805	1.2662

Stability Study

Accelerated stability study was performed as per ICH guidelines on best batch F3 to determine the change in physical characteristics, dissolution study and disintegration time of tablets on storage at 45^{o}C and 75% relative humidity for 3 months. Every month the sample was withdrawn and to evaluated for change in weight of tablets, hardness, friability, *In vitro* disintegration time, uniformity of drug content and dissolution, as shown in Table no 5.

Table 5: Stability study of best batch F3 at 45^{o}C and 75% RH.

Physical parameters	0 Days	30 Days	60 Days	90 Days
Weight Variation(mg)	150.56±0.64	150.72±1.19	151.49±1.78	152.47±1.34
Friability (%)	0.47±0.03	0.47±0.11	0.47±0.08	0.47±0.31
Disintegration Time (sec)	17.0±0.18	17.04±0.55	17.4±0.23	17.8±0.33
Drug Content (%)	99.11±0.50	99.04±0.23	98.01±0.20	98.34±0.11
Drug Dissolution (%)	98.03±1.56	98.70±3.41	98.50±2.54	98.01±2.45

RESULT

Preliminary SD gives the 91.49±0.033 to 94.34±0.519 drug content. The A3 has the more drug content 94.34±0.519 SD. Release profile of Lercanidipine with different carrier and ratios are shown in Figure 1.

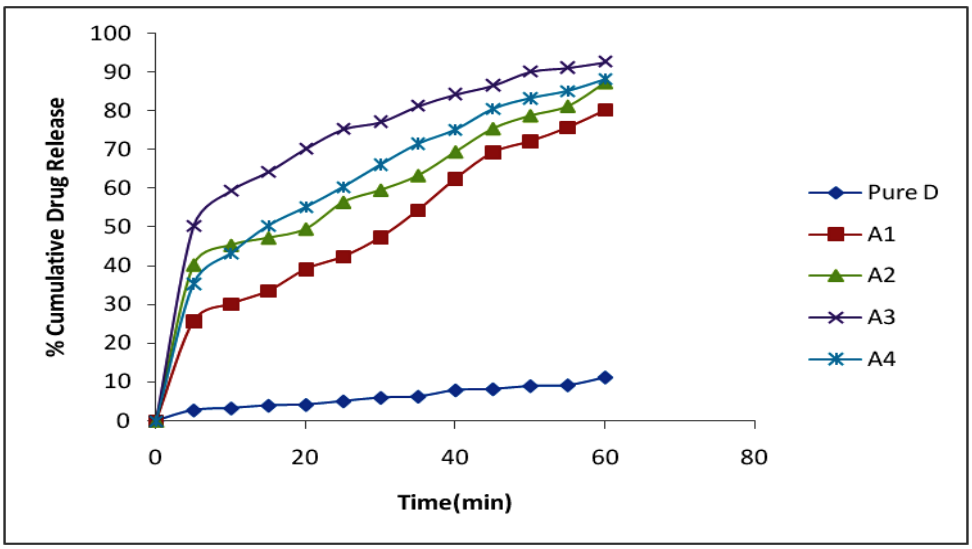

Figure 1: Drug Release Profile Solid Dispersion A1-14 and Pure Drug.

The percent drug release of the SDs is more than the pure drug and it significantly increase the solubility of Lercanidipine. The drug release of SD Granules was found between 80.11±1.34 to 92.56±1.11. Solid dispersion A3 of gives 92.56 drug releases. The combination SDs of the Polxmer 188 and Aerosil (1:4:2) was gives faster drug release with in 60 min. The DSC thermo gram of Lercanidipine exhibited a sharp endothermic peak at 178.8°C (Fig 2).

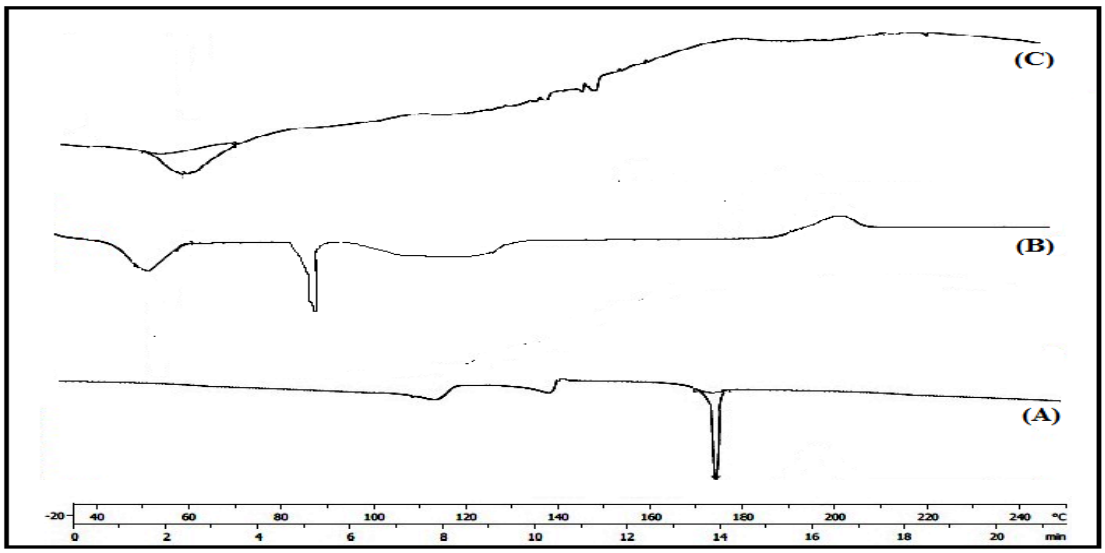

Figure 2: DSC Thermogram of (A) Pure Lercanidipine, (B) Solid Dispersion (C).

Physical Mixture with respect to its melting point and decomposition. The peaks in Fig 2 show broad endothermic peak at 90.14 ^{0}C this could indicates that the drug transits to amphorphous form due to solid dispersion.

The XRD pattern of Lercanidipine, SDs and physical mixture was shown in Fig.3.

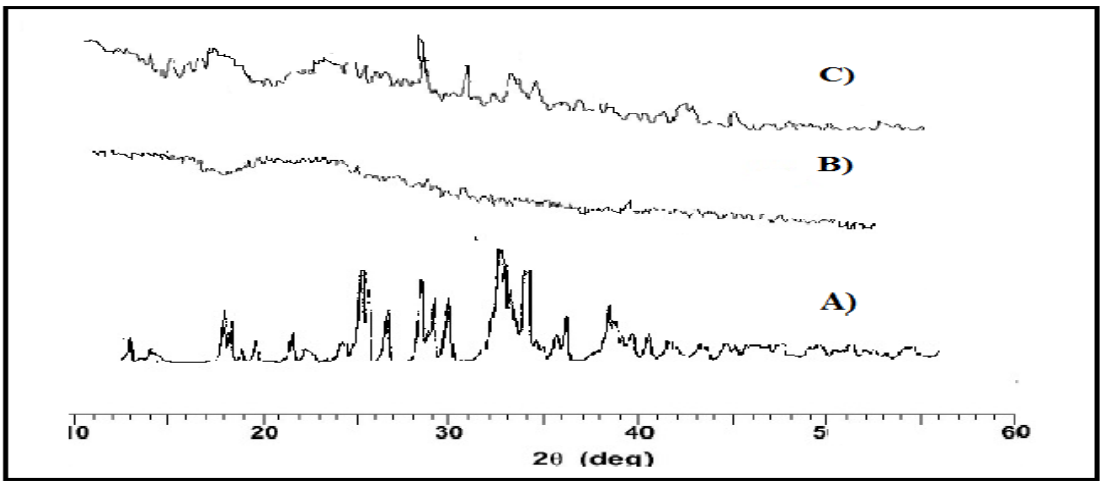

Figure 3: A) Lercanidipine B) Solid Dispersion C) Physical Mixture.

The pure Lercanidipine drug showed numerous sharp peaks demonstrating the crystalline nature of the drug. Lercanidipine showed characteristic intense peaks between the 2θ of 15^0 and 25^{0}due to its crystalline nature. Whereas, in case of solid dispersions crystallinity of lercanidipine was reduced to a greater extent as compared to physical mixture and pure lercanidipine, more over peak at 15^0 and 25^{0}were disappeared in solid dispersion. All the SD granules showed diffused peaks indicating that the drug is dispersed at the molecular level in the polymer matrix and hence, no crystals were found then the solid dispersion is amorphous.

All batches of the Lercanidipine tablets prepared by solid dispersion by direct compression method and were characterized for various physical parameters like weight variation, thickness, friability, drug content, wetting time, disintegration time and dissolution. Results were shown in Table 3. It was observed that the entire tablets meet the standard within the Pharmacopoeia limits. The present investigation was undertaken to formulate and evaluate fast dissolving tablets of Lercanidipine by Solid Dispersion method using Croscarmellose sodium and crospovidone and Sodium starch glycolate Superdisintegrants.

Formulation F1, F4, F7 which contain 4% Super disintegrants release the drug (94.06±1.42, 93.69±1.55, 94.93.01±2.12) respectively and in the release of drug found in formulation F2,

F5, F8 containing 6% Superdisintegrants release (96.01±1.56, 95.12±2.08, 95.45±1.98) and increase in the release of drug found in formulation F3,F6,F9 8% super disintegrant release the (98.03±1.59,96.03±1.68,96.07±2.09).

Drug release profile of the fast dissolving tablet formulation is shown in Fig 4.

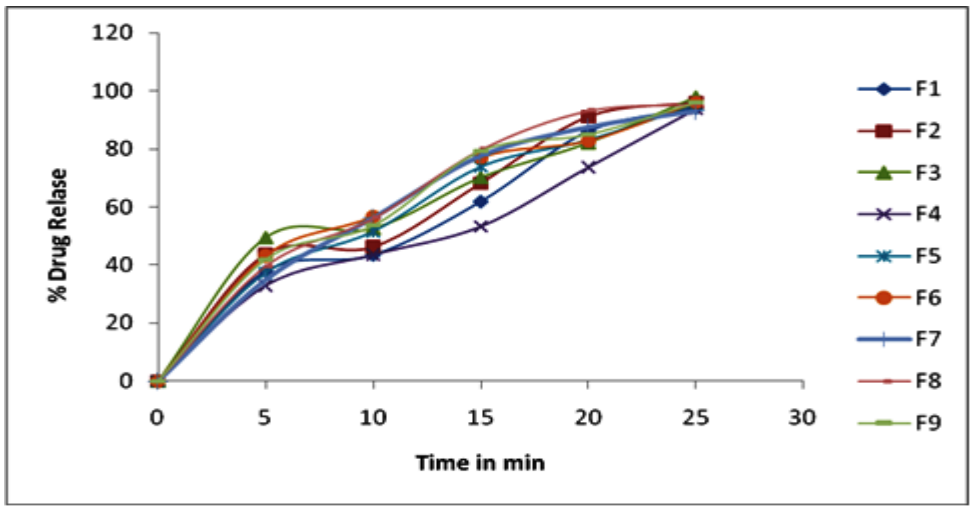

Figure 4: Dissolution Profile of Batch F1-F9.

After the studying different models, the zero order 'R' values was found to be range of 0.834 to 0.983, First order release in 'R' values ranges from 0.905 to 0.969 the higuchi's diffusion equation 'R' values of all formulations code ranges from 0.782 to 0845, Korsemeyer-pepp as plot was found in range of 0.783 to 0.845. The in-vitro drug release showed the highest regression coefficient values for first order model. The kinetic modeling data is mention in Table 4 First order is applicable to study hydrolysis kinetics and to study release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

After stability study of tablets, all the evaluation parameters of tablets was slightly and results was found within limits. The accelerated stability study of batch (F3) revealed that no significant change in physical properties and could be considered as stable formulation even after 3 months. The accelerated stability study of fast dissolving tablets was shown in Table 5.

DISCUSSION

All batches of the Lercanidipine tablets prepared by solid dispersion by direct compression method and were characterized for various physical parameters like weight variation,

thickness, hardness, friability, drug content, wetting time, disintegration time and dissolution. It was observed that the entire tablets meet the standard within the Pharmacopoeia limits. The percentage drug release of all the batches was found within the acceptable limits. The cumulative percentage of the drug released for formulation batch F3 found by the dissolution test shows the better drug release of 98.03±1.59 than the other formulation.

CONCLUSION

Fast dissolving tablets of Lercanidipine were prepared by direct Solid Dispersion method using Croscarmellose sodium, Sodium Starch Glycolate and crospovidone as a superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. In vitro drug release from the tablets shows significantly improved drug dissolution. It was concluded that in Fast dissolving tablet, crospovidone was best superdisintegrant. Hence it could be concluded that the superdisintegrant based fast dissolving tablets of Lercanidipine would providing quick onset of action without need of water for swallowing or administration.

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