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Research Article

FORMULATION, DEVELOPMENT AND EVALUTION OF SURFACE SOLID DISPERSION OF LARCANDIPINE FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT

Vaphare AM*, DR. Banerjee SK, Gadhave MV, DR. Gaikwad DD,

Department of Pharmaceutics

Vishal Institute of Pharmaceutical Education and Research, Ale.

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ABSTRACT:

The aim of †the present study was to improve lercanidipine HCl solubility and in vitro dissolution rate by preparing solid dispersion with using the solvent evaporation technique. Solid dispersions with Sodium starch glycolate (SSG), Crospovidone (CP) and Croscarmellose sodium (CCS) (as carriers) were prepared in drug: carrier (1:2, 1:4, 1:6, 1:8, and 1:10) ratios along with the corresponding physical mixtures. Analytical techniques, FT-IR spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) were used to characterize the drug in the physical mixtures and solid dispersions. The solubility and wettability studies of solid dispersions as well as physical mixtures showed greater improvement compared to the pure drug. Higher in vitro dissolution of solid dispersions was recorded compared to their corresponding physical mixtures and the pure drug. Solid dispersion in 1:6 drug to carrier ratio exhibited the highest drug release (97 %) in comparison with solid dispersion in 1:6 drug to carrier ratio (97% drug release), whereas there was no significant improvement in dissolution of solid dispersion in drug to carrier ratio in comparison with its physical mixture. The FT-IR spectra suggested that there was no interaction between lercanidipine HCl and Methanol when prepared as a solid dispersion. No representative DSC peaks for drug were observed for solid dispersion indicating the transformation of crystalline structure of lercanidipine HCl. The absence of XRD peaks of the drug in solid dispersion demonstrated that drug was present in amorphous structure suggesting the transformation of crystalline form of lercanidipine HCl to amorphous form. This polymorphic transformation contributes to faster dissolution rate of solid. The dissolution efficiency values for pure drug and solid dispersion compared also support this aspect.

Keywords: *Lercanidipine HCl. Surface solid dispersion, Solvent evaporation, In vitro dissolution.*

INRODUCTION

Lercanidipine hydrochloride, a calcium-channel blocker, which is chemically 2[(3,3-diphenyl Propyl)methyl amino]-1,1-dimethylethylmethyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [1,2] (Fig.1). Its molecular formula is $C_{36}H_{41}N_3O_6HCl$ and molecular weight 648.19 g/mol.Lercanidipine hydrochloride is used for treatment of angina pectoris and hypertension. It inhibits cellular influx of calcium leading to the maintenance of the plateau phase of the action potential. It showed great efficacy in various clinical trials in the management of preoperative and postoperative pain associated with gynecological, orthopedic, abdominal and dental surgeries. [2] Lercanidipine is completely insoluble in water and slightly soluble in simulated gastric fluid. Its poor aqueous solubility [3] can makes its absorption dissolution rate limited and thus delay the onset of action. The dissolution of drugs is a prime determinant in the absorption of poorly water soluble drugs and also serves as a rate-limiting step. [4] Poor aqueous solubility can cause formulation related problems.

For corrospondance:
Vaphare Ashok M.
VJSM's, Department of Pharmaceutics,
Vishal Institute of Pharmaceutical Education & Research, Ale Tal. : Junnar, Dist.: Pune (412411)
Contact no.: 9987654212
Email id- **ashokvaphare@rediffmail.com**

Furthermore Lercanidipine showed polymorphism [5] could be one of the reasons for low aqueous solubility. The formulation of poorly water-soluble drugs is one of the most challenging tasks to the formulation experts. An enhancement in the solubility and the dissolution rate can improve the oral bioavailability of such drugs, which further improves the therapeutic efficacy and patient compliance. Various techniques have been used to enhance the solubility of poorly water soluble drugs including the use of surfactants [6] amorphous form of drug micronization [7] and solid dispersion [8-10] and inclusion complexation. The aim of the present study was to enhance the dissolution rate of solid dispersion techniques. Solid state characterization was done by using DSC, XRD and FTIR study. Furthermore inclusion complex were evaluated for saturation solubility and dissolution release rate study.

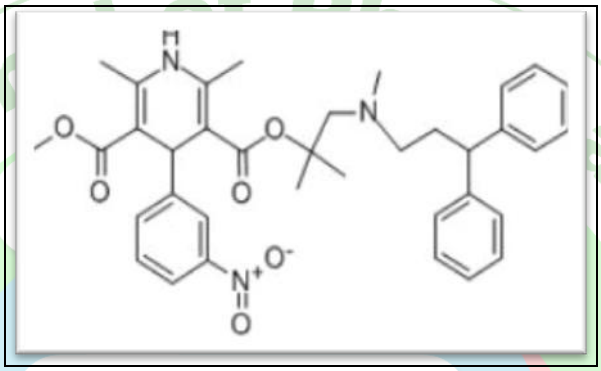

Figure 1: Chemical Structure of Lercanidipine Hcl

MATERIALS AND METHOD

Lercanidipine HCl (Glemnark, Navi Mumbai), Crospovidone (Polyplasdone XL-ISP, Hyderabad), Croscarmellose sodium (Ac-Di-sol, Colorcon), Sodium starch glycolate type-B (Colorcon), Ethanol and all the reagents used were analytical grade.

Preparation of Surface Solid Dispersion o f Lercanidipine:

Dissolve the required quantity of Lercanidipine in 10 ml Ethanol. Then disperse the accurately weighed quantity of carrier corresponding to different drug: carrier ratio by weight was dispersed into the drug solution. Allow to evaporate the solvent on water bath on stirring at temperature of 40-45^{0}C in proper environmental condition. Then this dried mass was passed through #100 meshes. The powder was subsequently dried at 40^{0}C for 3 hours in a tray drier and stored in desiccators for further studies.

Characterization of Surface Solid Dispersions (SSD):

Production yield:

Production yield was determined by following formula:

$$\text{Yield} = (a \times b + c) \times 100$$

Where,

a - Weight of solid dispersion sifted through # 100.

b - Weight of Lercanidipine taken for solid dispersion preparation,

c - Weight of polymer taken for solid dispersion preparation.

Assay:

Accurately weighed samples equivalent to 10 mg of drug was taken in a 100 ml volumetric flask, 10ml methanol was added and sonicated for 20 min to dissolve the drug. The volume was made to 100 ml with 0.1N HCl. The dispersion was filtered using Whatmann filter paper. A 10ml aliquot of the above solution was taken and diluted to 100ml with 0.1N HCl. The absorbance of sample solution was determined at 285 nm against acid blank.

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°C. Accurately samples (plain drug and surface solid) of drug 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 and filtered through Whatman filter paper and diluted to 10 ml with 0.1N HCl. Sink conditions were maintained throughout the study. The samples were then analyzed at λmax of 240 nm by UV/visible spectrophotometer.

FTIR Spectroscopy

About 1mg of sample was mixed with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer USA Spectrum 65 IR spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 400 cm-1 in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

Powder X-Ray Diffraction Analysis:

To understand XRD pattern of pure drug and optimized formulation, a Philips 1710 X-ray Diffractometer (XRD) with a copper target and nickel filter was used to obtain XRD result for the samples. Powder were mounted on aluminum stages with glass bottoms and smoothed to a level surface. The XRD pattern of each sample was measured from 10 to 50 degrees 2-theta using a step increment of 0.1 2 theta degree and a dwell time of 1 second at each step.

Differential Scanning Calorimeter:

DSC was performed in order to assess the thermo tropic properties and thermal behavior of the drug (lercanidipine). About 2 mg of the sample were sealed in the aluminum pans and heated at the rate of 5°C /min, was recorded by using "Perkin-Elmer differential scanning calorimeter with a pyris workstation", by covering a temperature range of 20°C to 250°C under nitrogen atmosphere of flow rate 30ml/min

Solvent Residue:

The determination of methanol was performed by gas chromatography on a Agilent GC 6890N with 7694E Head space sampler, fitted with flame ionization detector. Carrier gas was nitrogen. Headspace GC is used to detect solvent residues. The packed column was BD-624 capillary column. Temperature of oven was 60°C injection port 140°C and detector 250°C. Oven was programmed at 5°C/min for 10min, 15°C/min up to 250°C with a hold time of 7 min.

Table 1: Coding formulations for Surface solid dispersion of Lercanidipine

Drug		Lercanidipine	Lercanidipine	Lercanidipine
Carrier		SSG	CCS	CP
Code	1	SSD-S1	SSD-C1	SSD-P1
Code	2	SSD-S2	SSD-C2	SSD-P2
Code	3	SSD-S3	SSD-C3	SSD-P3
Code	4	SSD-S4	SSD-C4	SSD-P4
Code	5	SSD-S5	SSD-C5	SSD-P5
Drug: Carrier ratio	1	1:2	1:2	1:2
Drug: Carrier ratio	2	1:4	1:4	1:4
Drug: Carrier ratio	3	1:6	1:6	1:6
Drug: Carrier ratio	4	1:8	1:8	1:8
Drug: Carrier ratio	5	1:10	1:10	1:10

Table 2: Result of Production yield and Assay of Surface solid dispersion

Drug	Carrier	Code	Ratio	Production yield (%)	Assay (%)
LERCANIDIPINE	Sodium starch glycolate	SSD-S1	1:2	95.21	96.35
		SSD-S2	1:4	93.78	90.32
		SSD-S3	1:6	97.62	98.92
		SSD-S4	1:8	91.53	102.03
		SSD-S5	1:10	92.75	95.38
	Croscarmellose Sodium	SSD-C1	1:2	95.05	94.55
		SSD-C2	1:4	94.68	92.97
		SSD-C3	1:6	96.65	97.22
		SSD-C4	1:8	92.43	91.56
		SSD-C5	1:10	96.01	98.33
	Crospovidone	SSD-P1	1:2	96.05	98.84
		SSD-P2	1:4	93.70	96.32
		SSD-P3	1:6	88.62	94.91
		SSD-P4	1:8	96.77	91.66
		SSD-P5	1:10	95.01	97.64

Table 3: Comparison studies of dissolution profiles of different SSD in 0.1 N HCL

Code	D:C ratio	T5	T10	T15	T30	T60	T90
SSD-S1	1:2	14.64	25.53	31.6	37.65	47.73	57.21
SSD-S2	1:4	18.24	28.83	40.8	41.13	46.53	52.56
SSD-S3	1:6	25.56	32.04	42.48	65.45	82.61	92.67
SSD-S4	1:8	12.45	20.63	33.85	51.55	60.13	75.63
SSD-S5	1:10	19.89	32.16	42.51	56.01	65.43	69.33
SSD-C1	1:2	21.66	27.51	37.83	46.89	69.06	78.69
SSD-C2	1:4	19.11	29.66	35.57	51.33	72.09	88.86
SSD-C3	1:6	25.06	41.86	62.59	77.62	91.53	97.5
SSD-C4	1:8	22.56	35.65	49.07	65.88	76.51	82.26
SSD-C5	1:10	10.1	14.5	18.97	22.5	30.01	37.02
SSD-P1	1:2	25.20	44.30	59.50	64.48	74.93	78.60
SSD-P2	1:4	15.09	25.60	31.60	40.06	47.57	56.13
SSD-P3	1:6	30.12	60.59	65.89	75.60	83.90	93.98
SSD-P4	1:8	23.45	54.10	62.70	72.20	78.20	83.40
SSD-P5	1:10	20.50	47.00	59.10	68.60	79.36	82.26

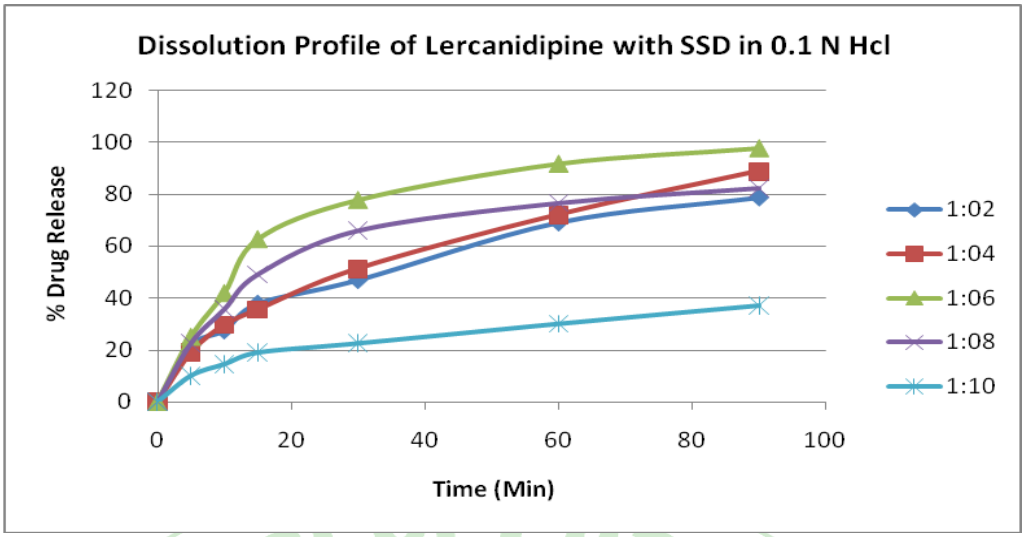

Figure 2: Dissolution Profile of Lercanidipine with SSD in 0.1 N Hcl

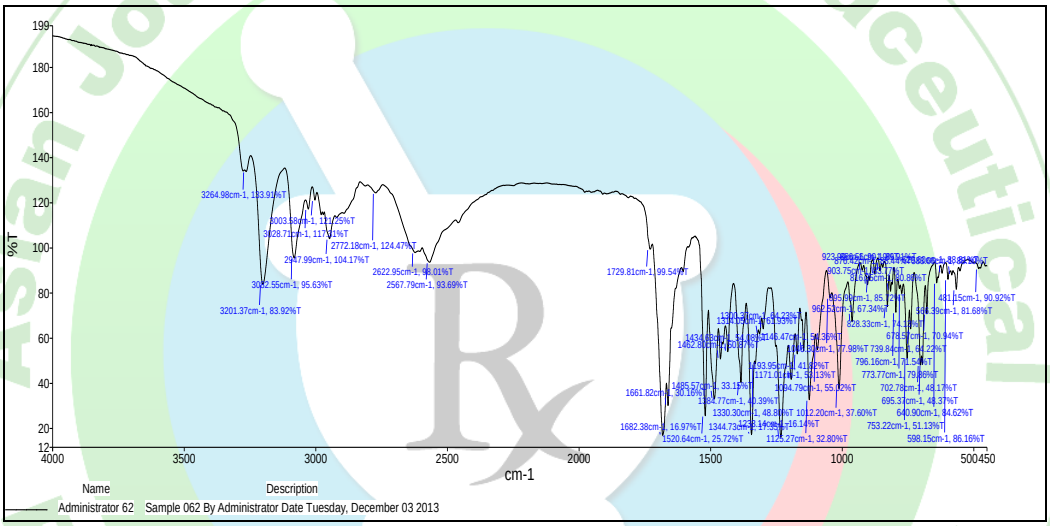

Figure 3: IR Spectra of Lercanidipine

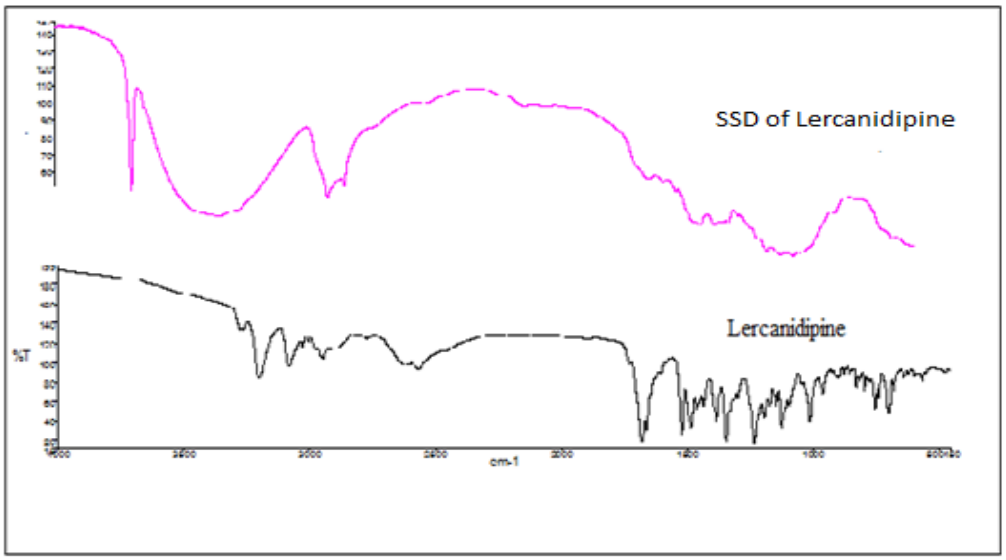

Figure 4: IR spectra of Lercanidipine and SSD of Lercanidipine

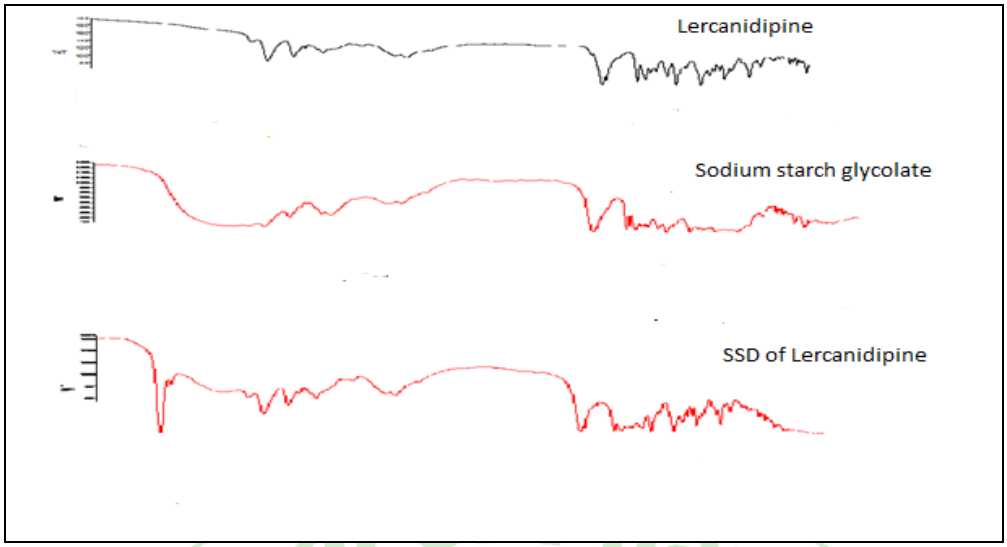

Figure 5: Comparative IR spectra of Lercanidipine, Sodium starch Glycolate and SSD of Lercanidipine

CONCLUSION

Lercanidipine as a low mean oral bioavailability and is virtually insoluble in water. It is because of all these problems that the drug is formulated as solid dispersions as to release it effectively. Finally, based on the above study it was concluded that the solid dispersion technique was shown to be a successful approach for improving the dissolution rate of Lercanidipine. The nature and amount of carrier used played an important role in the enhancement of the dissolution rate. The increased solubility and dissolution rate of Lercanidipine provided the rapid onset of action.

The order of increase in dissolution rate with various super-disintegrant is SSG>CCS>CP. This surface solid dispersion could then be incorporated successfully into a capsule or tablet, either in conventional or sustain release formulation. Among the super disintegrant tested SSG gave highest enhancement of dissolution rate and efficiency of Lercanidipine (1:6 ratio). In each case the dissolution rate and drug release were increased as the concentration of carriers in the surface solid dispersions were increased.

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