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Research Article

FABRICATION AND ASSESSMENT OF LERCANIDIPINE HYDROCHLORIDE SOLID DISPERSIONS FOR SOLUBILITY PREFERMENT USING POLYMER COMBINATION

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ABSTRACT

Objective: An attempt has made in fabricating solid dispersions (SDs) by taking lercanidipine hydrochloride (LCD) as a model drug.

Methods: The SDs were made using a poly mix of poly vinyl pyrrolidone (PVP) K-30, Poloxamer-188, and hydroxy propyl methyl cellulose (HPMC) K4M. Different proportions of LCD: polymer mix in 1:1, 1:3, 1:5, and 1:7 ratios were fabricated as SDs by solvent evaporation and melting method, further compressed into tablets. The LCD SDs were assessed for physicochemical, and LCD release possessions.

Results: The results were observed to be attractive with the increase in solubility LCD SD (F-3 and F-7) with 1:5 ratios of LCD.

Conclusion: The study concludes that the poly mix of PVP K-30, Poloxamer-188, and HPMC K4M and was found to be a better combination for elevating the solubility and release of LCD from the SDs.

Keywords: Lercanidipine, Polymer, Solid dispersions, Dissolution.

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INTRODUCTION

The oral route is ideal, for its ease of handling and intake by patients of all ages [1]. Solubility and dissolution are vital constraints for drugs with poor solubility [2]. Formulation scientist makes several attempts to resolve the issues related to solubility.

Various approaches were made to elevate the drug solubility, among them solid dispersions (SDs) approach positioned on the peak [3], as it is a simple, easy, and efficient tactic in increasing solubility.

Lercanidipine hydrochloride (LCD) is a calcium channel blocker, which is of BCS Class II with t ½ of 8h and 10% bioavailability [4]. LCD is prescribed for hypertension and angina patients. The poor aqueous solubility of LCD restricts the onset of action [5]. The antihypertensive action of LCD is because of a direct relaxing of vascular smooth muscle which lowers total peripheral resistance and henceforth blood pressure [6].

The authors attempted to elevate the solubility of LCD by SD approach using the combination of water-soluble polymers. In this investigation, Poly Vinyl Pyrrolidone (PVP) K-30, Poloxamer-188, and Hydroxy Propyl Methyl Cellulose (HPMC) K4M were employed in combination. These carriers play an auspicious role in growing the solubility of LCD. In the current research, the SDs were made by melting and solvent evaporation approaches.

MATERIALS AND METHODS

Materials

LCD was a kind sample from Torrent Pharmaceuticals, Mumbai. PVP K-30, Poloxamer-188, HPMC K4M, Microcrystalline Cellulose, Talc, and Magnesium stearate were procured from SD Fine Chemicals India. Double distilled water was used whenever desirable.

Designing of SDs

The various formulae of LCD, SDs are illustrated in Table 1.

Designing of SDs

Melting

The polymers were melted on their melting point basis (HPMC-K4M, PVP K-30, finally Poloxamer-188) in a porcelain dish; later LCD was dispersed in the formed mass with continual blending [7]. The blend was solidified at room temperature. The product was stored in a desiccator (ABG Initiatives, Hyderabad, Telangana) for a day, later crumpled in a mortar (Aruna Scientific, Hyderabad, Telangana) with little force. The formed powder was passed through the # 60 sieve (ASTM E 11, Hyderabad, Telangana) to get even-sized particles.

Solvent evaporation

LCD and the polymer mix (PM) were taken (Table 1), dissolved in dichloromethane (DCM), and stirred until the DCM evaporated utterly. The attained bulk was shifted to Cal. Chloride containing desiccators until it dries totally [8]. The solid mass obtained was then rumpled in a mortar and passed through the # 60 sieve and stored in a desiccator till use.

Fabricating of SD tablets

The SD equivalent to 20 mg of LCD was made by direct compression into tablet form [9], after blending with constituents (Table 2) compressed in the eight station tablet compression machine (Karnavati, India).

Evaluation

Melting point

The drugs are available in the purest form. The preliminary test for assessing LCD purity was the determination of its melting point using the melting point apparatus (MT-934, Mumbai) [10]. The temperature at which LCD melts was recorded in triplicate.

Solubility studies

LCD pure drug was tested for solubility in 0.1N HCl, water, pH 4.5 Acetate buffer, pH 6.8, and pH 7.4 Phosphate buffers [11].

Drug-excipients compatibility studies

The differential scanning calorimetry (DSC) and Fourier-transform infrared (FTIR) studies were made to confirm the interaction between the LCD and the carriers used in formulating SDs.

DSC

A 1:1 ratio of LCD: PM (~20mg) was placed in DSC crucible and heated from 50°C to 300°C in DSC apparatus (DSC-50, Shimadzu, Japan).

FTIR spectroscopic study

The relations between constituents of the SDs were confirmed by scanning in FTIR spectroscopy. The FTIR spectra of the LCD and in mixture with carriers were recognized by the FTIR spectrometer (Bruker) by scanning at 4000-400 cm^{-1}.

Evaluation LCD SDs

The obtained SDs were examined for the mentioned parameters [12,13].

Flow properties

The SDs were evaluated for flow constraints (angle of repose, densities, Carr's Index, and Hausner's ratio).

Yield

The % recovery includes the weight of dried SDs to the total weight of constituents used utilized in making SDs.

$$\% \text{ Yield} = \frac{\text{Actual weight of the SD}}{\text{Total weight of drug and excipients}} \times 100$$

Characterization of tablets made with SD

The SDs were compressed into tablets and were assessed for the valuations, illustrated as follows [14-17].

Uniformity in size and shape

The SDs which were compressed into the tablets were scrutinized under a dissection microscope (DM-100, Mumbai) for their outer morphology.

Thickness

The tablets were held between the jaws of Vernier Calipers (Qumos Enterprises, India), and breadth was examined thrice.

Table 1: Various formulae and codes

Drug:Carrier	Ratio	Method of preparation	Formulation code
LCD:PM	1:1	Melting	LSD-1
	1:3	Melting	LSD-2
	1:5	Melting	LSD-3
	1:7	Melting	LSD-4
LCD:PM	1:1	Solvent evaporation	LSD-5
	1:3	Solvent evaporation	LSD-6
	1:5	Solvent evaporation	LSD-7
	1:7	Solvent evaporation	LSD-8

PM: Polymer mix (Equal portion of PVP K-30+ Poloxamer-188+HPMC K4M)

Table 2: Formulae of SD tablets

Ingredients	Quantity per tablet
SD equivalent to 20 mg of LCD	150
Lactose	75
Starch	15
Micro crystalline cellulose	50
Magnesium stearate	5
Talc	5
Weight of the tablets	300

LCD: Lercanidipine hydrochloride

Uniformity in weight

20 tablets from every batch of tablets were separately weighed with an electronic digital balance (Citizen, CY-104, Mumbai, India), and the mean was calculated. The deviation was measured and then intersects with IP limits (±5% for 300 mg tablet).

Hardness and friability

The tablets were pressed between the two poles of the Pfizer tablet hardness tester. The force to break the tablets was recorded thrice. Surface attrition may transpire while tablet handling can be illuminated by Roche Friabilator. 10 tablets weighed ($W_{initial}$), positioned, and allowed to fall from a height of 6 inches for 4 min at 25 rpm, later the final weight of tablets (W_{final}) was taken. The weight loss of tablets was assessed as follows.

$$F = \frac{\text{W initial} - \text{W final}}{\text{Winitial}} \times 100$$

Calibration curve

100 mg of LCD dissolved in pH 1.2 solution (0.1M HCl). A series of dilutions (2, 4, 6, 8, and 10 µg/ml) were prepared scanned spectrophotometrically at 239 nm then the absorbance versus concentrations gives a calibration curve.

Uniformity of drug content

The prepared tablets (10 numbers) were powdered, mixed, and an equivalent of 20 mg LCD was dissolved in methanol, diluted and the absorbance was measured at λ_{max} of 239 nm. The tablets obey the test, only if each content deceits between 85% and 115% of the mean content.

In vitro drug release studies

The USP paddle apparatus with 900 ml 0.1N HCl, which was revolved at 50 rpm, and maintained at 37±0.5°C. Samples were withdrawn at 10, 20, 30, 40, 50, and 60 min and filtered using Whatman filter paper and diluted to 10 ml with 0.1N HCl, and analyzed at λ_{max} of 239 nm by UV/visible spectrophotometer.

RESULTS AND DISCUSSION

LCD melts at 197.8±1.84°C show the purity of the LCD, as the pure form melts in between 196°C and 198°C. The LCD showed good solubility in 0.1N HCl (0.311±0.028 µg/ml) comparatively in Water, Acetate buffer (pH4.5), Phosphate buffer (pH6.8), and Phosphate buffer (pH7.4). The solubility data for pure LCD are illustrated in Fig. 1.

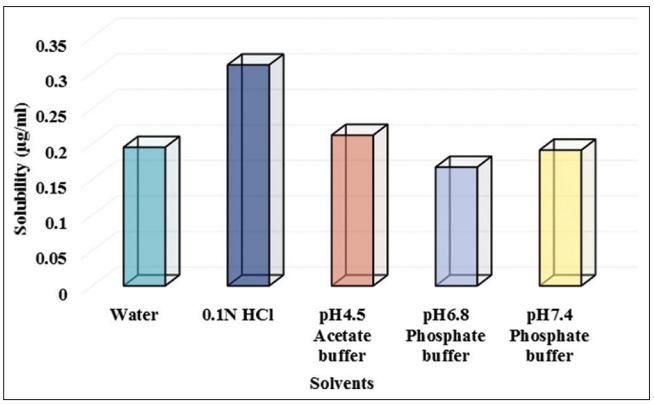

Fig. 1: Solubility of pure lercanidipine hydrochloride in various solvents

The DSC thermograms of LCD with PM were moved to the left and reduced which indicates a definite mingling of LCD with polymers adopted (Fig. 2).

The FTIR study disclosed that the typical peaks and stretches of LCD pure drug were also found in LCD-PM indicates no negative incompatibility of LCD with carriers used. The FTIR spectra of LCD pure and polymers are shown in Fig. 3.

On the other hand, the LCD, SDs showed the angle of repose between (25° and 30°), that is, 25.69±0.65 and 29.95±0.53°, which confirms excellent flow properties. On the other hand, the compressibility index was <10 and the Hauser ratio <1.09, representing good compression assets while tableting. The flow properties of LCD-SDs are concise in Table 3.

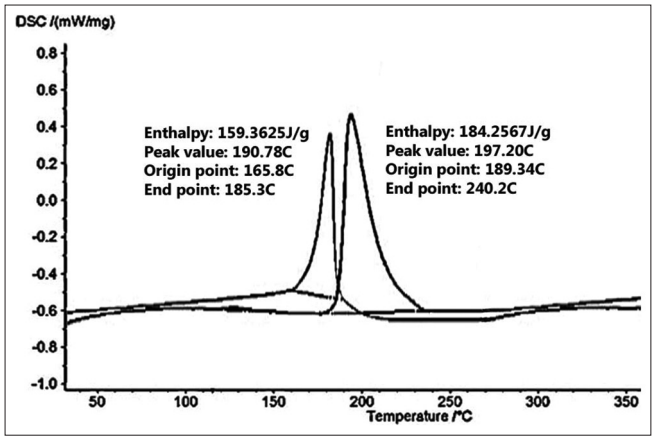

Fig. 2: Differential scanning calorimetry thermograms of lercanidipine hydrochloride pure and with polymer mix

The yield of LCD-SDs was observed to be good (>90%), and LSD-7 has a good yield of 99.3±1.58%, the LCD-SDs tablets appeared to have a uniform size, shape, pale white-colored, and odorless with a smooth surface.

The tablets were found to have a uniform thickness, ranged from 5.00±0.01 to 5.05±0.02 mm, and weight. The loss on friability was <1% (0.29±0.02–0.68±0.02%), and the hardness was >4 Kg/cm^2 (5.9±0.05–8.2±0.06) indicating that the tablets bearing considerable mechanical strength and the LCD content were also found to be uniform. All these values are illustrated in Table 4.

The solubility of LCD was found to be good in 0.1N HCl and decrease with an increase in the pH of the buffer. Among them, LSD-7 represented good solubility in 0.1 N HCl. The entire explanation of solubility is represented in Fig. 4.

LCD followed Beer's Lambert's law at 2–10 µg/ml. The regression R^2 value was observed to be 0.9994 with a slope of 0.0785×+0.0411. The LCD was determined by plotting the calibration curve of the LCD (Fig. 5).

LCD released from the tablet was initially by burst <10 min and at the end of 1 h the LCD was completely released. The dissolution of prepared tablets was found good in formulations with LCD: PM at the ratio of 1:5 (Fig. 6), which followed zero order.

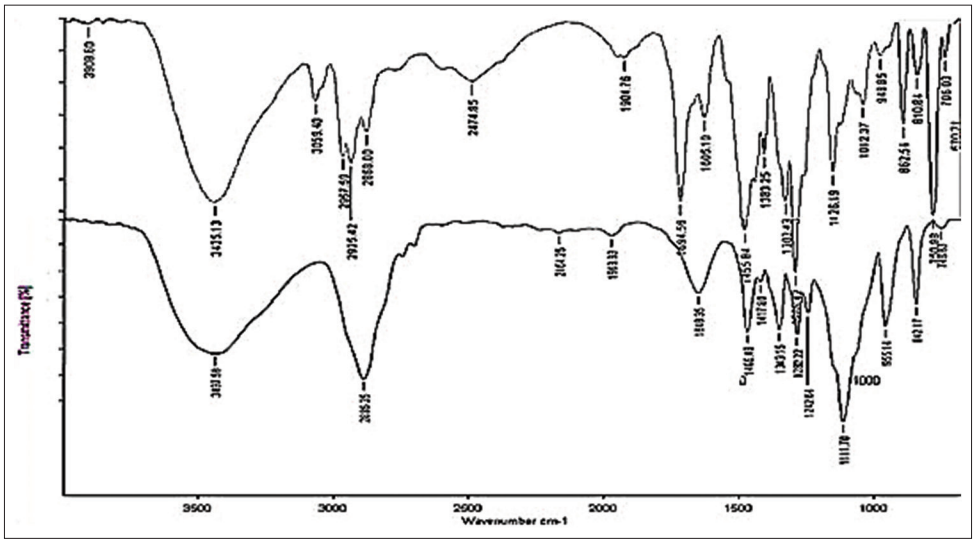

Fig. 3: Fourier-transform infrared spectra of lercanidipine hydrochloride and blend

Table 3: Flow character specifications

Formulation	Flow properties				
	Angle of repose (°)	Bulk Density	Tapped Density	Carr's Index	Hauser Ratio
LSD-1	27.86±0.48	0.462±0.02	0.498±0.02	7.228±0.01	1.077±0.04
LSD-2	25.69±0.65	0.492±0.01	0.501±0.03	1.796±0.01	1.018±0.08
LSD-3	29.48±0.32	0.501±0.02	0.522±0.01	4.022±0.03	1.041±0.05
LSD-4	25.92±0.32	0.468±0.03	0.485±0.02	3.505±0.02	1.036±0.01
LSD-5	26.39±0.95	0.492±0.02	0.509±0.03	3.339±0.01	1.034±0.05
LSD-6	27.27±0.57	0.528±0.01	0.539±0.02	2.040±0.01	1.020±0.03
LSD-7	29.95±0.53	0.565±0.04	0.588±0.04	3.911±0.02	1.040±0.06
LSD-8	27.65±0.42	0.554±0.05	0.577±0.03	3.986±0.01	1.041±0.02

Values in mean±SD; trials made (n=3), LCD: Lercanidipine hydrochloride

Table 4: Physical characteristics of prepared SDs

Formulation	Physical parameter					
	Yield (%)	Thickness (mm)	Uniformity of weight (mg)	Hardness (cm2)	Friability (%)	Assay (%)
LSD-1	90.2±0.95	5.05±0.02	300.1±1.54	6.9±0.12	0.29±0.02	94.6±1.84
LSD-2	93.3±0.59	5.01±0.03	300.7±2.87	7.2±0.05	0.42±0.03	95.5±2.52
LSD-3	96.1±1.34	5.04±0.01	301.3±6.84	6.7±0.02	0.51±0.04	94.8±2.85
LSD-4	94.0±2.25	5.02±0.01	300.1±2.92	8.2±0.06	0.68±0.02	93.7±1.06
LSD-5	93.8±1.15	5.03±0.01	300.2±1.90	5.9±0.05	0.49±0.03	97.5±2.32
LSD-6	95.5±1.65	5.04±0.02	300.7±1.68	6.2±0.06	0.37±0.01	95.2±1.65
LSD-7	99.3±1.07	5.00±0.01	300.5±2.07	7.6±0.02	0.54±0.02	99.7±1.69
LSD-8	94.5±1.25	5.01±0.02	301.4±3.98	7.1±0.02	0.62±0.01	98.4±2.35

Values in mean ±SD; trials (n=3), LSD: Lercanidipine hydrochloride, SD: Solid dispersions

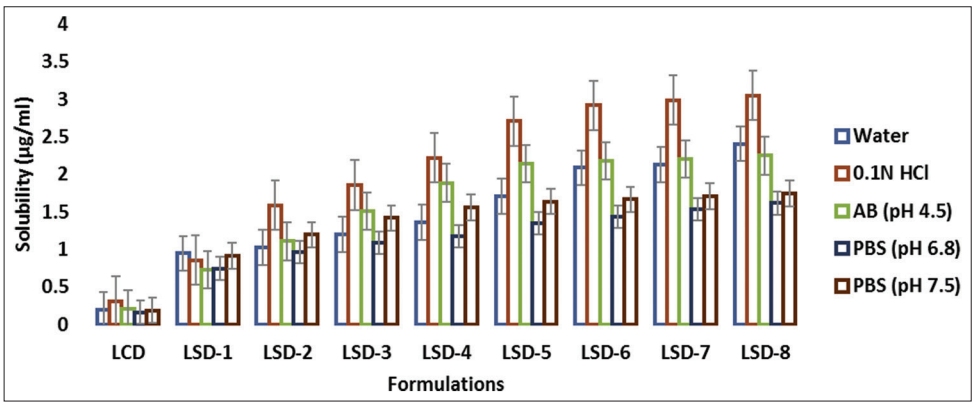

Fig. 4: Solubility of lercanidipine hydrochloride and solid dispersions in various buffers

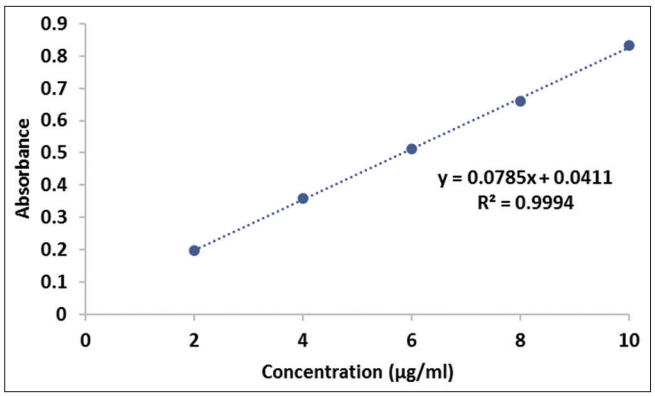

Fig. 5: Calibration curve of lercanidipine hydrochloride

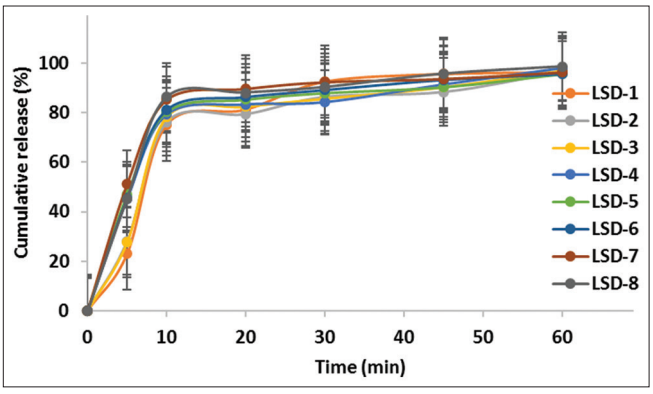

Fig. 6: *In vitro* drug dissolution plots of lercanidipine hydrochloride solid dispersions

CONCLUSION

The study revealed that the combination of PVP K-30. Poloxamer-188 and HPMC-K4M carriers were good carriers for increasing the solubility of Lercanidipine by fabricating them as SDs. The F-7 formulation with 1: 5 proportions of Lercanidipine and the carrier mix prepared by the melting approach was good in increasing the *in vitro* dissolution of Lercanidipine.

AUTHORS CONTRIBUTION

Nazemoon Reddy was carried out the work. Swarnalatha Dugasani and Devanna Nayakanti were directed the project.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest related with this work.

AUTHORS FUNDING

Nil.

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