Design & Characterization of Lercanidipine HCl Microcrystalline Formulation for Solubility & Dissolution Enhancement

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Abstract— **Improved bioavailability is an added advantage for most of the poorly water soluble drugs. In recent years research work is concentrated on various methods to improve the solubility characteristics of poorly soluble drugs and crystallization phenomenon is one amongst them. The solubility problem can be solved by changing the crystal habit of drug, which improves the solubility and dissolution. So, in the present investigation an attempt has been made to improve the solubility characteristics of Lercanidipine Hcl an anti-hypertensive drug, using solvent change method. In this method drug was dissolved in organic solvent (ethanol) to form organic phase. Aqueous phase was prepared by dissolving stabilizing agents in water. Cross carmellose sodium used as stabilizing agents. The formulated crystals of Lercanidipine Hcl were subjected to various physico-chemical parameters like size distribution, solubility studies, in-vitro dissolution studies, drug content, solvent interactions with FT- IR. The microcrystals produced with cross carmellose sodium showed better dissolution as compared to pure drug and microcrystals formulated using MC. FTIR results showed that there was no interaction between the drug, solvent and the stabilizer.**

Keywords: - Microcrystals, Lercanidipine Hcl, Cross carmellose sodium, ethanol.

I. .INTRODUCTION

A common observation throughout the pharmaceutical industry is that as the potency and specificity of new drug candidates are improving, the poor aqueous solubility is often becoming a problem. This may result in poor bioavailability of the active pharmaceutical ingredients. Given the increasing number of compounds emerging from discovery programs having poor aqueous solubility and/or dissolution, pharmaceutical scientists are constantly seeking new formulation approaches in order to obtain an adequate oral bioavailability[1]. Several techniques are commonly used to improve dissolution and bioavailability of poorly water soluble drugs, such as size reduction[2], the use of surfactants[3], the formulation of solid dispersions[4], complexation with cyclodextrins, and the transformation of crystalline drug to amorphous state[5]. In addition to the general solubility enhancement techniques described above, drug particle size reduction has often been used, in regards to the Noyes–Whitney and Ostwald– Freundlich equations, to enhance dissolution of poorly water soluble compounds[6]. Particle size reduction is achieved because adsorption of excipients onto the particle surface that inhibits particle growth[7]. Particle size can be reduced and formulated into micro-crystals. Crystal morphology may be altered by preferential adsorption of stabilizing agent onto specific faces of the growing crystal[8]. Crystallization is a phenomenon in which solid particles formed by solidification under favorable conditions of a chemical element or a compound, whose boundary surfaces are planes symmetrically arranged at definite angles to one another in a definite geometric form. The polymorphic changes will have a definite influence on the solubility and thereby bioavailability of a particular compound due to structural differences resulting from different arrangements of molecules in the solid state. Lercanidipine Hydrochloride is a long-acting dihydropyridine CCB[9] with high vascular selectivity, and thus has many of the characteristics that are desirable in an antihypertensive agent. Lercanidipine Hcl microcrystals were developed by solvent change precipitation method. The microcrystals were evaluated by studies like FTIR.

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II. LITERATURE REVIEW

1. Mr. Mohan Kumar et. al. has made formulation to improve the solubility characteristics of Lercanidipine HCl an anti-hypertensive drug, using solvent change method. In this method drug was dissolved in organic solvent (methanol) to form organic phase. Aqueous phase was prepared by dissolving stabilizing agents in water. Poloxamer-407 (1%) and Polyvinyl pyrollidone K30 (1.1%) are used as stabilizing agents.
2. Ms. Ruchi Jain et. Al. has developed formulation having the use of hydrotropic solution which She has shown that, it may be a proper choice to preclude the use of organic solvents so that, a simple, accurate, novel, safe and precise method could be developed for estimation of poorly water soluble drug, lercanidipine hydrochloride. Solubility of lercanidipine hydrochloride (LER) is increased by using 2M citric acid as hydrotropic agent
3. Ms. Dipti S. Maheshwari et. al. formulate and evaluate the effect of increasing Lercanidipine HCl on the characteristics of fast-disintegrating sublingual tablets by solubility enhancement as Lercanidipine HCl undergoes first pass metabolism in liver and gut wall which has oral bioavailability of approx 10-20%.
4. Mr. Pandey Suneel et. al. has improved lercanidipine HCl solubility and in vitro dissolution rate by preparing solid dispersion with polyethylene glycol (PEG) 6000 using the solvent evaporation technique. The solubility and wettability

studies of solid dispersions as well as physical mixtures showed greater improvement compared to the pure drug.

5. Mr. Dr. Asija Rajesh et. al. has shown the significant effect of malonic acid on enhancement of solubility of lercanidipine hydrochloride by simple solvent change process has been demonstrated. The optimised cocrystal formulation exhibited enhancement in aqueous solubility. simple solvent change process has been demonstrated.

III. MATERIALS & METHODS

A. *Preparation of LER Microcrystals*

Microcrystals of LER (F_1, F_2 and F_3) were prepared by solvent change method[10] using cross carmellose sodium. Briefly, a fixed amount of LER (300 mg) was dissolved in up to 10 ml of ethanol. This organic phase was added at room temperature, under constant mechanical stirring (600 rpm) to 100 ml of 1:2, 1:4 and 1:6 w/v aqueous solution of cross carmellose sodium. Stirring was continued for 30 min. Microcrystals were collected after filtration, washed with deionized water and dried at room temperature.

B. *Preparation of LER Physical mixture*

Physical mixtures of LER (P_1, P_2 and P_3) were prepared by mixing LER with cross carmellose sodium. A fixed amount of LER (300 mg) was dissolved in up to sufficient of ethanol and triturated with 100 ml of 1:2, 1:4 and 1:6 w/v aqueous solution of cross carmellose sodium in a mortar. It was continued for 30 min.

TABLE I
FORMULATION OF LER MICROCRYSTALS & PHYSICAL MIXTURE

Ingredients	LER Microcrystals			LER Physical mixture		
	F_1	F_2	F_3	P_1	P_2	P_3
Lercanidipine (mg)	300	300	300	300	300	300
Stabilizing agent	CCS	CCS	CCS	CCS	CCS	CCS
stabilizing agent (gm)	0.6	1.2	1.8	0.6	1.2	1.8
Organic solution (ml)	5	6	8	5	6	8
Stirring speed (rpm)	600	600	600	--	--	--
Temp (°C)	25	25	25	25	25	25

LER = Lercanidipine Hcl, CCS = Cross Carmellose Sodium.

C. *Percentage Yield*

The practical percentage yield was calculated from the weight of dried microcrystals (Practical mass) to the initial weight (Theoretical mass) & the results are reported in the percentage yield was calculated by using the following formula[11]

$$\%\ Yield = \frac{practical\ mass}{theoretical\ mass} \times 100$$

D. *Drug Content*

A weighed quantity of the microcrystals was dispersed in 100 ml of 0.1 M Hcl. 1ml of resultant solution was withdrawn and diluted to 10 ml. The above solution was analyzed by UV-Visible Spectrophotometer (Agilent Technologies, carry 60 UV-Vis, Japan) at 241nm. It was carried out in triplicate.

E. *Solubility studies*

The solubility of Lercanidipine microcrystal's in water was determined by taking excess quantity of microcrystals and adding to 100 ml volumetric flask filled with water and sonicated. The solution was filtered through whatmann filter paper and the drug concentration was determined spectrophotometrically at 241 nm[12].

F. *Particle size determination*

Particle size of the prepared microcrystals was determined by optical microscopy. The optical microscope was fitted with an ocular micrometer and a stage micrometer. The eyepiece micrometer was calibrated. The particle diameters of more than 100 microcrystals were measured randomly by optical microscope[13].

The average particle size was determined by using the Edmondson's equation:

$$Dmean = \frac{\sum nd}{\sum n}$$

Where, n – Number of microcrystal's observed
d – Mid point range.

G. *In-vitro dissolution study*

The in vitro dissolution studies were carried out using USP type II dissolution apparatus (Rotating Basket type). The dissolution study was carried out in 0.1M Hcl solution of pH 1.2. The dissolution medium was kept in a thermostatically controlled water bath, maintained at 37 ± 0.50 C. The rotation of basket was set to 75 rpm. At predetermined time intervals between 0 and 80 min, 5ml of dissolution medium was withdrawn and analyzed for the drug release at 241 nm. At each time of withdrawal, 5ml of fresh corresponding dissolution medium was replaced into the dissolution flask. The samples withdrawn were analyzed by UV method at 241 nm against blank.

H. *IR study*

In order to check the integrity (compatibility) of drug in the formulation, FT-IR spectra of the microcrystals formulations with that of pure drug were compared (using IR carry 630 spectrophotometer) using potassium bromide (KBr).the samples were thoroughly blended with dry powdered KBr crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The FT-IR spectra of the

formulation were compared with the FT-IR spectrum of the pure drug.

I. Stability study

The selected formulations were packed in the containers and are tightly closed with the cap. They were stored at the stated conditions for one month[15]. Samples were analyzed after 30 days and they were evaluated for drug content.

IV. RESULTS

TABLE II
DRUG CONTENT & SOLUBILITY OF LER MICROCRYSTALS & PHYSICAL MIXTURE

Parameter	LER Microcrystals			LER Physical mixture		
	F_1	F_2	F_3	P_1	P_2	P_3
Drug content (%)	62.76	64.60	61.60	63.00	69.20	61.60
Solubility (µg/ml) ± SD	50.70 ± 0.001	75.76 ± 0.002	60.73 ± 0.001	63.76 ± 0.002	68.58 ± 0.002	62.87 ± 0.002

TABLE III
PARTICLE SIZE ANALYSIS OF LER MICROCRYSTALS & PHYSICAL MIXTURE

Particle size (µm)	LER Microcrystals			LER Physical mixture		
	F_1 (1:2)	F_2 (1:4)	F_3 (1:6)	P_1 (1:2)	P_2 (1:4)	P_3 (1:6)
0-10	4	6	9	7	8	6
10-20	48	44	50	50	55	45
20-30	40	38	30	35	30	38
30-40	5	12	7	5	5	7
40-50	3	2	4	3	2	4
Average Particle size (µm)	20.50	21.50	19.10	19.70	18.90	20.70

TABLE IV
% DRUG RELEASE PROFILE OF LER MICROCRYSTALS & PHYSICAL MIXTURE

Time (min)	LER Microcrystals % Drug release			LER Physical mixture % Drug release		
	F_1	F_2	F_3	P_1	P_2	P_3
10	25.07	25.54	28.77	23.76	24.63	26.28
20	30.52	31.64	33.21	23.87	26.47	26.95
30	38.58	40.97	39.28	35.43	31.17	32.83
40	51.63	56.60	52.37	39.84	38.05	38.73
50	60.78	68.24	62.65	34.10	43.01	47.19
60	69.02	76.34	70.64	47.64	48.05	51.72
70	80.63	82.99	79.25	52.40	59.79	55.75
80	91.46	95.35	90.09	57.70	65.05	59.28

TABLE V
STABILITY STUDY OF LER MICROCRYSTALS & PHYSICAL MIXTURE

Stability condition	LER Microcrystals	LER Physical mixtures	Physical stability No. of days 10	Drug content (%) LER Microcrystals	Drug content (%) LER Physical mixtures
Ambient (5°C)	F_1	P_1	No change in Appearance	61.60	65.74
	F_2	P_2		64.76	69.24
	F_3	P_3		61.60	64.89
Room temp 25°C / 60% RH	F_1	P_1	No change in Appearance	61.56	65.76
	F_2	P_2		64.76	69.22
	F_3	P_3		61.59	64.90
Higher temp 40°C/ 75% RH	F_1	P_1	No change in Appearance	61.57	65.73
	F_2	P_2		64.75	69.21
	F_3	P_3		61.58	64.87

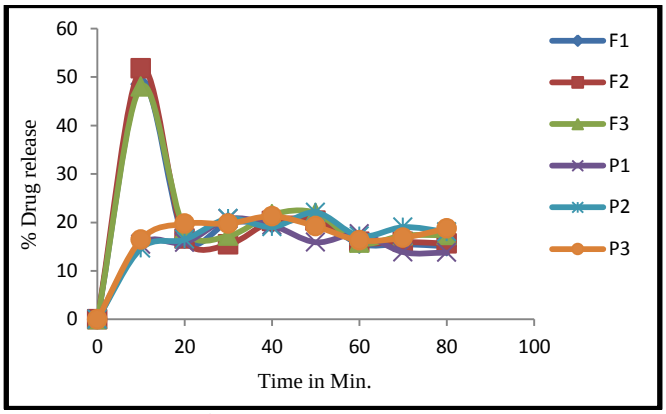

Fig. 1 % Drug release of LER Microcrystals and Physical mixture

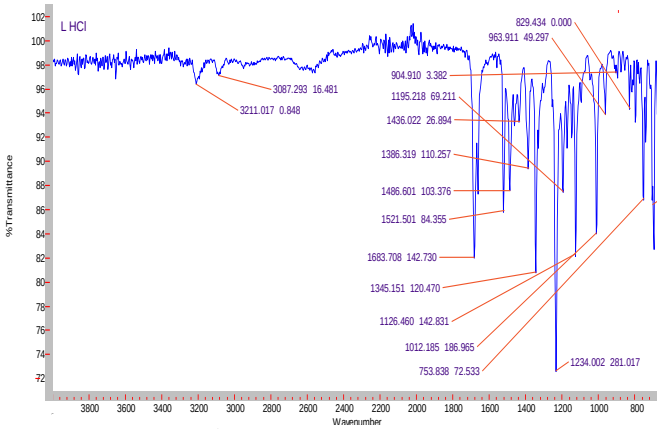

Fig. 2 FT-IR Spectrum of Lercanidipine Hcl

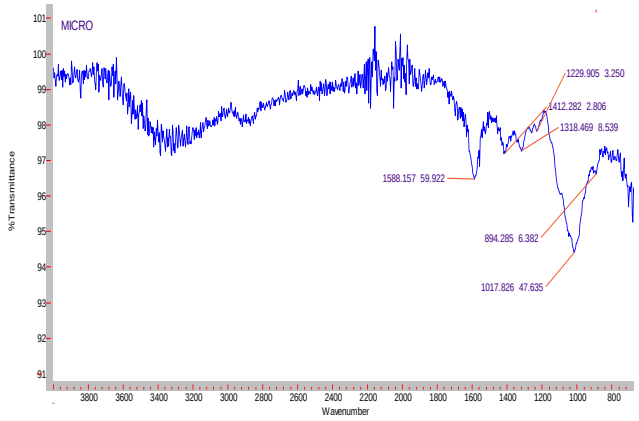

Fig. 3 FT-IR Spectrum of Prepared LER Microcrystals (F_2)

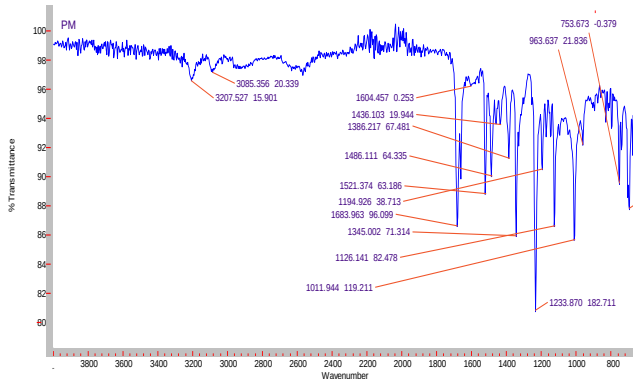

Fig. 4 FT-IR Spectrum of Prepared LER Physical Mixture (P_2)

V. Discussion

Preparation of LER Microcrystals:-

Microcrystals & Physical mixtures of Lercanidipine Hcl were prepared by solvent change method using hydrophilic binders as stabilizing agent. The selection of a good solvent depends on the miscibility with water and the solubility of drug in that solvent. Different proportion of stabilizing agent: solvent was selected and microcrystals were prepared at 600 rpm as shown in TABLE I. A first requirement for a stabilizing system is that it provides wetting of the hydrophobic surfaces of the drug particles. Surfactants used in the preparation of microcrystals stabilized these particles and avoided its growth. The solvent change method for preparation of microcrystals was found to be efficient.

Drug Content:-

The drug content was found to be good and uniform among the different formulations of the prepared samples and was found to be 61.60 to 69.20 % as shown in TABLE II.

Solubility:-

As water is a universal solvent, apparent solubility studies were carried out in deionized water. In solubility studies of the samples, the microcrystals (F_2) prepared using cross carmellose sodium have showed highest solubility of the drug in water (75.76 ± 0.002µg/ml) as compared with the physical mixture P_2 (68.58 ± 0.002) as shown TABLE II.

Particle size determination:-

Particle size determination was carried out for prepared microcrystals and physical mixtures as shown in TABLE III.

Dissolution Studies:-

The dissolution profiles of the prepared microcrystals and the physical mixtures are illustrated in TABLE IV & fig. 1. Prepared microcrystals showed the faster dissolution rate, with approximately more than 50% of the drug being released within 40 min compared to approximately 39 % for the physical mixture. At the end of 80 min, more than 90 % of the drug was released from all crystals except for the physical mixture. This effect can be explained by an increased specific surface area which is hydrophilized due to the adsorbed hydrophilic polymers. Increase in solubility may be due to optimum amount of stabilizing agent was used and because of reduction in size, hydrophilicity of stabilizing agent, better solubility and wettability of microcrystals.

Stability Studies:-

Stability studies were performed as per ICH guidelines. The results indicated that there was no evident change in the physical appearance of formulations at the end of the 10 days storage period at 5°C / ambient, 25° C / 60% RH & 40° C / 75% RH conditions. The drug content of F_2 and P_2 at the end of 10 days for 5°ambient was 64.76% and 69.24% respectively, for 25° C/ 60% RH was 64.76 % and 69.22% respectively, for 40° C/ 75% RH was 64.75% and 69.21% respectively as shown in TABLE V.

FT-IR study:-

The FTIR studies indicated that there is no strong interaction at molecular level when compared formulations to pure drug as spectrum shown in fig. 2, 3 and 4.

VI. Conclusion

Microcrystals of Lercanidipine Hcl were prepared by solvent change technique. From the above discussion it has been concluded that the prepared Microcrystals of Lercanidipine Hcl exhibited good solubility, dissolution rate and physicochemical properties in comparison to that of the pure drug. The FTIR studies indicated that there is no strong interaction at molecular level. Hence microcrystals of the drug can be filled in capsules or formulated as tablets of Lercanidipine Hcl by direct compression in order to achieve enhanced solubility and improved bioavailability of the drug

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