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PREPARATION AND *IN-VIVO* EVALUATION OF LERCANIDIPINE HYDROCHLORIDE SOLID DISPERSIONS

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Abstract:

Lercanidipine hydrochloride is a BCS class II anti-hypertensive drug with poor solubility and low bioavailability of about 10%. Solid dispersion preparation through solvent evaporation technique was proven to enhance the solubility and bioavailability of this drug. In the present study, Kolliwax GMS and Gelucire 44/14 were used in the ratio of 1:3 with SLS and have shown highest solubility. Dissolution studies of optimized formulation S20 showed highest drug release of 99.08% at the end of 90 minutes among all formulations. From In vivo bioavailability studies C_{max} of the lercanidipine optimised solid dispersion 1715.317±1.45 ng/ml was significant ($p<0.05$) as compared to the pure drug suspension formulation 564.88±1.75 ng/ml. T_{max} of both optimised solid dispersion formulation and pure drug was 1.0±0.4 and 1.5±0.5 h, respectively. $AUC_{0-\infty}$ infinity for lercanidipine optimised solid dispersion formulation was higher (6190.64±1.42 ng.h/ml) than the pure drug suspension 2046.54±1.67 ng.h/ml. Statistically, AUC_{0-t} of the optimised solid dispersion formulation was significantly higher ($p<0.05$) as compared to pure drug suspension formulation. Higher amount of drug concentration in blood indicated better systemic absorption of lercanidipine from optimised solid dispersion formulation as compared to the drug suspension formulation. Thus, it can be concluded that Lercanidipine solid dispersions are one of the promising methods to increase its solubility and bioavailability.

Keywords —Lercanidipine, Hypertension, Solid dispersions, Pharmacokinetics.

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I. INTRODUCTION

The main objective of this study is to increase the solubility and therefore the dissolution of LercanidipineHCl by dispersion in various polymer matrices thereby choosing the best formulation. Lercanidipine hydrochloride is a BCS class II and an antagonist of L-type calcium channels. It is selective and specific towards smooth vascular cells. It is an active antihypertensive agent and thus useful for the treatment of angina and coronary diseases (Luscher et al., 1998). Because of lipophilic character, lipophilic drugs tend to concentrate in lipid containing membranes and slowly released to reach L-type calcium channel targets. Thus there is a slow onset and longer duration of action of the drug (Barchielli et al., 1997). Lercanidipine being a hydrochloride salt is given orally and is absorbed well from the upper gastrointestinal wall. However, the drug undergoes extensive first pass metabolism.

Lercanidipine exhibits polymorphism and is present as a mixture of crystalline and amorphous forms (Sawant et al., 2012). The polymorphic property is very important as it influences the solubility, absorption and therapeutic effect of final formulation (Hancock et al., 1997). Lercanidipine is a poorly water-soluble drug. Enhancement of drug dissolution in water is one of the challenging

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aspects of drug development. Numerous techniques have been developed to increase solubility and bioavailability of drugs. They are complexation with polymers, size reduction to micron range, solubilisation, and modification of physical form, prodrug formulations, derivatization of drugs and other techniques (Garad, 2004).

Solid dispersions are formulated with a hydrophilic matrix and a hydrophobic drug (crystalline or amorphous). The drug is dispersed in a fine crystalline or amorphous form in the matrix. When the solid dispersion is exposed to aqueous media, the carrier dissolves, dispersing the drug as fine colloid particles (Chiou et al, 1971). Thus the dissolution rate and bioavailability of poorly water soluble drugs are enhanced owing to the increased surface area (Ford et al, 1986).

II.MATERIALS AND METHODS

Materials

Lercanidipine Hydrochloride pure drug was a generous gift from MSN Laboratories Pvt. Ltd, Hyderabad, India. We bought Kolliphor P 407 and Kolliphor P188 from BASF in Mumbai. The supplier of Kolliwax GMS was Signet Chemical Corp. Pvt. Ltd. in Mumbai.Gelucire 44/14 was given by Gattefosse, France. Solupluswas gifted by BASF, Germany. Urea, Mannitol, PEG 4000 andPVP K-30 and were gifted from Dow Chemicals, USA. All other chemicals used were of analytical grade.

Preliminary solubility studies of Lercanidipine Hydrochloride

Solubility measurements of LercanidipineHydrochloridewere performed according to a published method reported by Higuchi and Connors in 1965 (Chen et al, 2007). An excess amount of Lercanidipine Hydrochloride was added to 25ml of aqueous solution of water soluble carriers like Urea, PEG4000, Soluplus, Kolliwax GMS, Kolliphor P 407 and Kolliphor P188, Mannitol, Gelucire 44/14 and PVPK-30 in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution was diluted properly with methanol. The diluted solution was then analysed for the Lercanidipine Hydrochloride in UV visible spectrophotometer at 240 nm.

Preparation of Lercanidipine Hydrochloride solid dispersion by the solvent evaporation method

The calculated amount of Lercanidipine Hydrochloride and the employed polymers (Soluplus, KolliwaxGMS II, Kolliphor P 407 and Kolliphor P188 and Gelucire 44/14) in different drug-polymer ratios (1:1 and 1:3) besides SLS as surfactant (0 or 2%) (as shown in Table 1) were weighed and mixed together in a porcelain dish. Twenty different formulae were prepared by the solvent evaporation method. The smallest quantity of methanol, a typical solvent, was used to dissolve the combination. The solvent was then completely evaporated in an oven at a temperature of 50°C. The prepared solid dispersions were sieved after being ground in a mortar. The fraction of the powder that passed through 45 µm was stored in a desiccator and used for further investigations.

Evaluation of Lercanidipine Hydrochloride solid dispersions

Percentage Practical Yield

Percentage practical yield was calculated using reported method (Lakshmi et al., 2012).

Drug content estimation

The percentage drug content in physical mixtures and solid dispersions was estimated by dissolving 20 mg quantities of physical mixtures and solid dispersions in methanol, followed by mixing thoroughly by shaking and finally the volume was made-up to the mark with solvent (0.1N HCl) (Poovi et al., 2013). The solution was filtered and the filtrate was diluted suitably with 0.1N HCl (1.2) pH and absorbance was measured at 240 nm using UV/Visible spectrophotometer (Patel et al., 2011).

Dissolution studies

Dissolution studies were performed using USP apparatus II. (Mandal et al., 2010) Pure drug and all the other products prepared as described earlier were included in this study. Samples of each

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TABLE 1
Composition of LercanidipineHCl solid dispersion

Formulation code	Lercanidipine HCl (gm)	Soluplus (gm)	Kolliphor P 407(gm)	Kolliwax GMS (gm)	Kolliphor P 188(gm)	Gelucire 44/14	SLS (gm)	Methanol (mL)
SD 1	0.2	0.2	-	-	-	-	0%	Qs
SD 2	0.2	0.2	-	-	-	-	2%	Qs
SD 3	0.2	0.6	-	-	-	-	0%	Qs
SD 4	0.2	0.6	-	-	-	-	2%	Qs
SD 5	0.2	-	0.2	-	-	-	0%	Qs
SD 6	0.2	-	0.2	-	-	-	2%	Qs
SD 7	0.2	-	0.6	-	-	-	0%	Qs
SD 8	0.2	-	0.6	-	-	-	2%	Qs
SD 9	0.2	-	-	0.2	-	-	0%	Qs
SD 10	0.2	-	-	0.2	-	-	2%	Qs
SD 11	0.2	-	-	0.6	-	-	0%	Qs
SD 12	0.2	-	-	0.6	-	-	2%	Qs
SD 13	0.2	-	-	-	0.2	-	0%	Qs
SD 14	0.2	-	-	-	0.2	-	2%	Qs
SD 15	0.2	-	-	-	0.6	-	0%	Qs
SD 16	0.2	-	-	-	0.6	-	2%	Qs
SD 17	0.2	-	-	0.2	-	0.2	0%	Qs
SD 18	0.2	-	-	0.2	-	0.2	2%	Qs
SD 19	0.2	-	-	0.6	-	0.6	0%	Qs
SD 20	0.2	-	-	0.6	-	0.6	2%	Qs

*Composition is for 10 doses.

preparation equivalent to 20 mg of drug were spread over the surface of the dissolution medium (900 ml of phosphate buffer at pH (6.8) maintained at a temperature of 37±0.5 ^{o}C, stirring at 50 rpm (Howlader et al., 2012). The samples were withdrawn at predetermined time intervals, filtered, diluted with methanol and analyzed using a UV spectrophotometer at 238 nm. Each test was performed in triplicate (Yang et al., 2015).

Stability studies

Prepared solid dispersions were placed inside sealed 40cc HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75%±5%RH and temperature of 40 ^{0}C±2^{0}C for stability studies. Samples were removed after 1, 2 and 3 months and evaluated for % drug content and in vitro dissolution studies (Dhirendra et al., 2009).

III. RESULTS AND DISCUSSION

Preliminary solubility studies of Lercanidipine Hydrochloride

When making solid dispersions, a preliminary examination of solubility was conducted in order to choose the best water soluble carriers, and the solubility of the pure medication was discovered to be 0.0516±0.008 mg/ml(Table 2). From this study, drug and Kolliwax GMS along with Gelucire 44/14 in the ratio of 1:1:1 have shown highest drug solubility i.e. 0. 2581±0.102 mg/ml, almost 5-fold increase compared to that of pure drug. For all the water soluble carriers used in preliminary solubility studies, PEG 4000, PVP K30, Mannitol and Urea have shown low solubility when compared with other carriers and did not included in the preparation of Lercanidipine Hydrochloride solid dispersions. The graphical representation of solubility studies of

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LercanidipineHydrochloridephysical mixtures is shown in Figure 1.

TABLE 2
Preliminary solubility studies of Lercanidipine Hydrochloride in different polymers

Physical Mixture	Solubility(mg/ml)
Pure Drug	0.0516±0.008
Drug + Urea	0.0655±0.003
Drug + Kolliwax GMS	0.1992±0.113
Drug + Mannitol	0.0721±0.001
Drug + Kolliphor P 188	0.1652±0.014
Drug + PEG 4000	0.0922±0.051
Drug + Kolliphor P 407	0.1672±0.007
Drug + PVP K 30	0.0812±0.112
Drug + Soluplus	0.1838±0.021
Drug + Kolliwax GMS + Gelucire 44/14	0. 2581±0.102

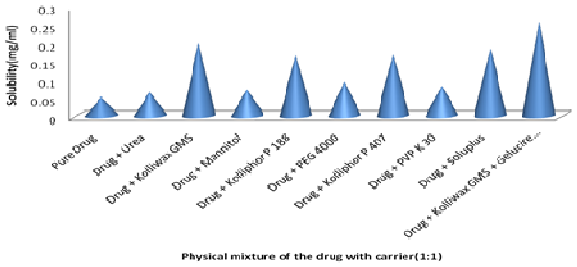

Fig. 1 Solubility studies of Lercanidipine Hydrochloride physical mixture

Evaluation Parameters

Solubility studies of LercanidipineHydrochloride solid dispersions

Different formulations of Lercanidipine Hydrochloride solid dispersions were prepared by solvent evaporation method with their respective carriers. After solids dispersion preparation, a solubility study was performed.The formulation (SD20) with Drug, Kolliwax GMS and Gelucire 44/14 in the ratio of 1:3 and with SLS shown highest solubility i.e. 0.7226±0.12mg/ml, almost 14 fold compared to that of the pure drug (Pure drug solubility is 0.0516±0.008 mg/ml). The results are tabulated in Table 3 and graphical representation is shown in Figure 2.

Percent Practical yield and drug content

The results of percent practical yield for all formulations of solid dispersions found to be 81.99±0.012% - 99.23±0.129%. The results of % practical yield studies and actual drug content are shown in Table 4. Maximum yield was found to be 99.23±0.129% for formulation SD20. The drug content of the prepared solid dispersions was found to be in the range of 84.57±0.004 – 99.03±0.138%. Maximum percent drug content i.e. 99.03±0.138 % was found in the formulation SD20.

TABLE 3
Solubility studies of Lercanidipine Hydrochloride solid dispersions prepared by solvent evaporation method

S. No.	Formulation code	Solubility (mg /ml) *
1	Pure drug (Lercanidipine)	0.0516±0.008
2	SD1	0.4211±0.017
3	SD2	0.4351±0.103
4	SD3	0.4555±0.221
5	SD4	0.4689±0.018
6	SD5	0.3205±0.002
7	SD6	0.3355±0.031
8	SD7	0.3407±0.021
9	SD8	0.3512±0.004
10	SD9	0.4955±0.031
11	SD10	0.5119±0.004
12	SD11	0.5269±0.011
13	SD12	0.5379±0.032
14	SD13	0.2581±0.004
15	SD14	0.2735±0.013
16	SD15	0.2898±0.041
17	SD16	0.3046±0.017
18	SD17	0.5891±0.002
19	SD18	0.6212±0.013
20	SD19	0.6515±0.022
21	SD20	0.7226±0.122

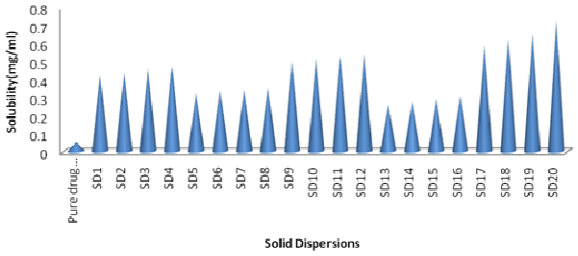

Fig. 2 Solubility studies of LercanidipineHydrochloridesolid dispersion

Percent Practical yield and drug content

The results of percent practical yield for all formulations of solid dispersions found to be 81.99±0.012% - 99.23±0.129%. The results of % practical yield studies and actual drug content are shown in Table 4. Maximum yield was found to be 99.23±0.129% for formulation SD20. The drug content of the prepared solid dispersions was found to be in the range of 84.57±0.004 – 99.03±0.138%.

Maximum percent drug content i.e. 99.03±0.138 % was found in the formulation SD20.

TABLE 4
% Practical yield and drug content for Lercanidipine Hydrochloride solid dispersions

S. No	Formulation	% Practical Yield	% Drug content
1	SD1	95.21±0.101	91.47±0.114
2	SD2	92.46±0.002	94.77±0.171
3	SD3	93.68±0.031	86.33±0.001
4	SD4	83.88±0.004	90.33±0.008
5	SD5	96.55±0.005	92.47±0.004
6	SD6	91.68±0.011	94.92±0.110
7	SD7	91.98±0.013	93.50±0.116
8	SD8	96.22±0.122	94.52±0.118
9	SD9	91.87±0.121	91.53±0.015
10	SD10	94.26±0.141	92.56±0.155
11	SD11	81.99±0.012	84.57±0.004
12	SD12	96.12±0.004	91.64±0.016
13	SD13	91.87±0.051	92.43±0.141
14	SD14	93.27±0.013	89.37±0.114
15	SD15	94.26±0.121	92.52±0.125
16	SD16	91.28±0.117	90.08±0.001
17	SD17	97 .23±0.009	96.01±0.182
18	SD18	98.23±0.1015	97.99±0.114
19	SD19	98.33±0.112	98.88±0.004
20	SD20	99.23±0.129	99.03±0.138

In vitro dissolution studies

The drug release data obtained for formulations SD1-SD20 shows the cumulative percent drug released as a function of time for all formulations. In vitro studies reveal that there is marked increase in the dissolution rate of Lercanidipine Hydrochloride from all the solid dispersions when compared to pure Lercanidipine Hydrochloride. From the in vitro drug release profile, it can be seen that formulation SD20 containing Combination of Dug, Kolliwax GMS and Gelucire 44/14 (1:3:3 ratio of drug: Kolliwax GMS and Gelucire 44/14 with surfactant) shows higher dissolution rate i.e. 99.08±2.9% compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The graphical representation of solid dispersions of SD1-SD8, SD9-SD14& SD15-SD20 with pure drug is depicted in Figures 3, 4 and 5.

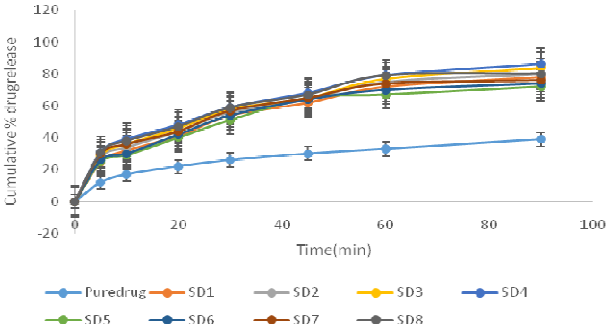

Fig. 3 In vitro dissolution profile of pure drug and different formulations of Lercanidipine Hydrochloridesolid dispersions (SD1-SD8)

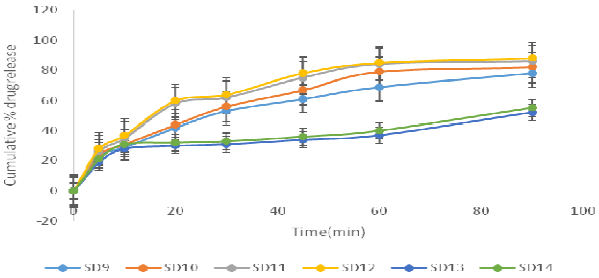

Fig. 4 In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (SD9-SD14)

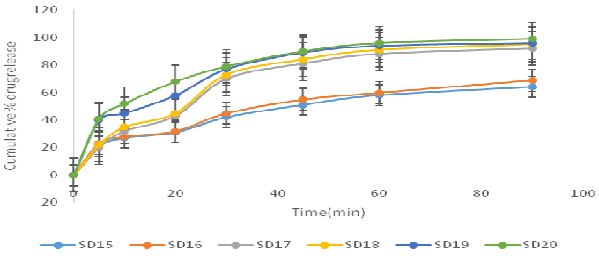

Fig. 5 In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride solid dispersions (SD15-SD20)

Stability studies

Optimized formulation (SD20) was selected for stability studies on the basis of high cumulative percent drug release. According to ICH recommendations, stability tests were carried out for drug content and in vitro drug release studies for 3 months at accelerated stability settings. The improved formulation remained stable for three months.From these results it was concluded that, optimized formulation (SD20) is stable and retained their original properties with minor differences which depicted in Table 5.

TABLE 5
Evaluation parameters of optimized formulation (SD20) stored at 40 ±2^{0}c /75 ±5%rh

Retest time for optimized formulation	% Drug content	*In-vitro* drug release (%)
0 days	99.03±0.138	99.08±2.9
30 days	98.11±0.101	98.85±1.1
60 days	97.01±0.008	98.15±0.1
90 days	96.14±0.116	97.35±1.7

Pharmacokinetic study of Lercanidipine solid dispersions

Pharmacokinetic studies of Lercanidipine

Animal preparation

Healthy Wistar rats were (Weighing 180-200 g) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25^{0}C, Relative Humidity 45% and 12 h alternate light and dark cycle) with 100 % fresh air exchanges in animals room, uninterrupted water and power supply. Rats were allowed to acclimatize to the environment for at least three days and supplied with a standard pellet diet and water ad libitum. The institutional animal ethics committee approved the protocol of animal study no**:**1292/ac/09/CPCSEA/47/A**.**

Study Design

Rats are divided in to 2 groups at randomly. The rats were fasted for 24 hours prior to the experiments(Deshpande et al., 2016). After 4 hrs of dose, food was reoffered. First group was administered with pure Lercanidipine (as such) made suspension with 0.5% methocel and second group was administered Prepared Lercanidipineoptimised solid dispersion diluted in 0.5% methocelby oral route at a dose of 0.3125 mg. Then, 200 µL blood samples were collected from the femoral artery at certain times 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24h post dose and transferred into Eppendorf tubes containing heparin in order to prevent blood clotting. Centrifugation at 3000 rpm for 5 minutes at room temperature was used to immediately produce the plasma. All samples were stored at 4°C until analysis.

Determination of Lercanidipine in Rat plasma by HPLC method

Chromatographic conditions

Shimadzu high performance liquid chromatography unit equipped with the LC-8A Solvent delivery module, SPD-10AVP UV-Visible spectrophotometer detector, Class CR-10 Data Processor, Rheodyne (with 20 µl capacity loop) Injection Port and Wakosil II C-18 Column (stainless steel column of 25 cm length and 4.6 mm internal diameter packed with porous silica spheres of 5 µ diameter, 100 Å pore diameter) were used for analysis of samples. The mobile phase consisted of acetonitrile and 0.1 M ammonium acetate buffer (pH 3.5) in a combination of 50:50 v/v. Before use the mobile phase was degassed by passing it through a 0.22 µm filter. The mobile phase was pumped at an isocratic flow rate of 1.2 ml·min-1 at room temperature. The UV-detection wavelength was set at 235 nm and sensitivity of 0.001 a.u.f.s was used for the analysis (Kumar Prasanna, 2008).

Pharmacokinetic analysis

Maximum plasma concentration (C_{max}), time to reach C_{max} (i.e., T_{max} and t ½values), area under the plasma concentration-time curve from zero to the last sampling time (AUC_{0-t}), and area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$).were the pharmacokinetic parameters used to evaluate. The linear trapezoidal method was used to compute AUC_{0-t}, and the formula below was used to obtain $AUC_{0-\infty}$

$$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$$

Win Nonlin 3.3® pharmacokinetic software was used to do a non-compartmental analysis on the pharmacokinetic parameters (Pharsight Mountain View, CA USA). The mean ± SD is used to represent all values.

Statistical analysis

With Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA), statistical analysis was carried out using one-way analysis of variance (ANOVA), followed by the Tukey-Kramer multiple comparison test.

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Differences that had a p-value of <0.05 were deemed statistically significant.

Discussion

Pharmacokinetic parameters were analyzed using standard, non-compartmental techniques. Maximum plasma drug concentration (C_{max}) and the time to reach this concentration (T_{max}) were determined from the plasma concentration-time curve.

Pharmacokinetic data of lercanidipine

Lercanidipine concentrations in plasma following oral administration of pure drug and optimized lercanidipine solid dispersion administered oral route are shown in Figures 6 & 7**.** The pharmacokinetic parameters were calculated as per the equations explained earlier and the results are shown in Table 6.

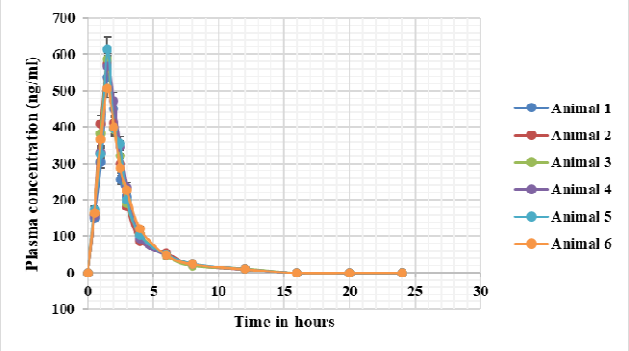

Fig. 6 Plasma concentration-time profile of lercanidipine pure drug in rat plasma

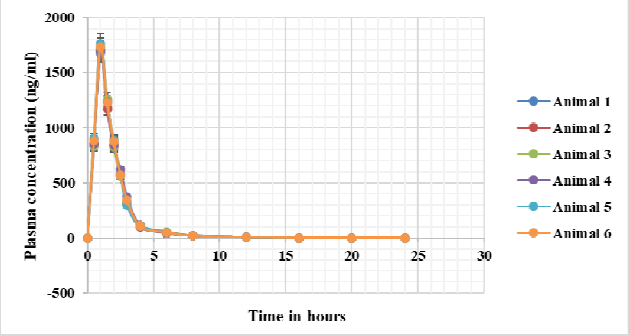

Fig. 7Plasma concentration-time profile of lercanidipine optimized optimised solid dispersion in rat plasma

Pharmacokinetic parameters comparison for lercanidipine pure drug and optimised solid dispersions

Figure 8indicates plasma concentration–time curve recorded post single oral dose of lercanidipine optimised solid dispersion formulation in comparison to lercanidipine pure drug suspension. At any time point, the drug plasma concentrations in animals administrated with optimised solid dispersion was higher than that of pure drug. (Table 7)

C_{max} of the lercanidipine optimised solid dispersion 1715.317±1.45 ng/ml was significant ($p<0.05$) as compared to the pure drug suspension formulation 564.88±1.75 ng/ml. T_{max} of both optimised solid dispersion formulation and pure drug was 1.0±0.4 and 1.5±0.5 h, respectively. AUC, which indicates the total integrated area under the blood concentration time profile and the total quantity of drug that enters the systemic circulation after oral delivery, is a crucial measure in assessing the bioavailability of a medication from a dose form. $AUC_{0-\infty}$ infinity for lercanidipine optimised solid dispersion formulation was higher (6190.64±1.42 ng.h/ml) than the pure drug suspension 2046.54±1.67 ng.h/ml. Statistically, AUC_{0-t} of the optimised solid dispersion formulation was significantly higher ($p<0.05$) as compared to pure drug suspension formulation. Higher amount of drug concentration in blood indicated better systemic absorption of lercanidipine from optimised solid dispersion formulation as compared to the drug suspension formulation (Figure 8).

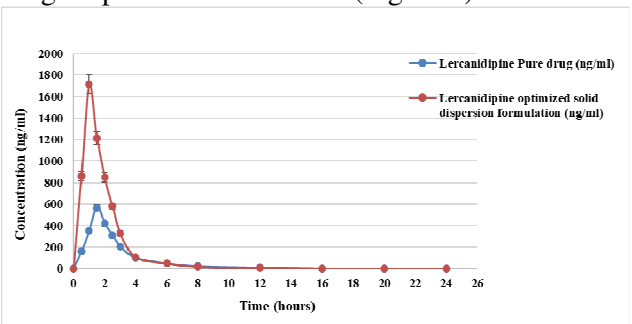

Fig. 8Plasma concentration profiles of lercanidipine optimised solid dispersion and pure drug

The pharmacokinetic data was subjected to statistical analysis to test the significant differences between the pharmacokinetic parameters of two

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formulations. The results are shown in Table 7. The data indicated that there was significant difference in C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, between lercanidipine pure drug and lercanidipine optimised solid dispersion formulation.

Kolliwax GMS and Gelucire 44/14 were used in the ratio of 1:3 with SLS and have shown highest solubility. Dissolution studies of optimized formulation S20 showed highest drug release of 99.08% at the end of 90 minutes among all formulations. From In vivo bioavailability studies

TABLE 6
Plasma concentrations of lercanidipine pure drug and lercanidipine optimized solid dispersion formulation in rat plasma

Time in hours	Plasma concentration (ng/mL) of pure drug							Plasma concentration (ng/mL) of lercanidipine solid dispersion optimised formulation						
	Rat							Rat						
	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Animal 6	Mean±s.d.	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Animal 6	Mean±s.d.
0	0	0	0	0	0	0	0±0	0	0	0	0	0	0	0±0
0.5	150.64	161.78	160.85	156.94	172.89	164.89	161.33±0.54	850.24	845.65	830.57	850.61	900.06	881.28	859.78±1.64
1	302.45	410.32	382.67	330.16	325.01	365.84	352.74±1.54	1675.45	1700.64	1726.36	1695.54	1764.55	1729.36	1715.317±1.45
1.5	538.21	574.42	586.27	568.04	615.24	507.1	564.88±1.75	1174.32	1168.83	1257.64	1232.28	1225.63	1227.15	1214.308±0.13
2	450.65	410.97	393.57	472.16	395.54	400.12	420.50±0.45	840.25	835.43	819.62	840.77	885.02	870.59	848.61±1.49
2.5	255.12	299.64	320.57	345.2	354.61	288.46	310.6±1.34	575.32	578.79	562.83	620.68	566.86	570.79	579.21±2.65
3	208.34	182.87	190.64	234.57	200.31	225.97	207.12±1.90	310.45	324.09	320.44	370.95	295.4	347.73	328.17±0.76
4	103.57	88.24	105.8	94.37	102.83	121.08	102.65±1.52	96.64	99.46	112.87	115.78	110.53	104.02	106.55±1.08
6	48.61	55.24	46.08	48.82	50.06	48.61	49.57±1.94	45.19	42.94	55.89	49.26	47.82	47.22	48.05±1.13
8	22.49	21.84	19.54	24.6	25.17	23.66	22.88±1.22	18.45	19.67	17.35	16.95	19.25	18.65	18.38±0.017
12	10.23	9.77	11.29	9.64	10.08	10.01	10.17±1.84	5.84	5.88	5.24	6.41	6.08	5.62	5.85±0.018
16	0.17	0.19	0.24	0.18	0.2	0.22	0.2±0.45	0.1	0.15	0.1	0.08	0.09	0.08	0.1±0
20	0	0	0	0	0	0	0.1±0	0	0	0	0	0	0	0±0
24	0	0	0	0	0	0	0±0	0	0	0	0	0	0	0±0

TABLE 7
Pharmacokinetic Parameters of lercanidipine optimised solid dispersion formulation and pure drug

Pharmacokinetic parameters	lercanidipine pure drug	lercanidipineoptimised solid dispersion
C_{max} (ng/ml)	564.88±1.75	1715.317±1.45
AUC_{0-t} (ng.h/ml)	1742.78±2.64	5336.84±1.97
AUC_{0-inf} (ng.h/ml)	2046.54±1.67	6190.64±1.42
T_{max}(h)	1.5±0.5	1.0±0.4
$t_{1/2}$ (h)	6.4±1.57	4.02±1.03

IV. CONCLUSION

Lercanidipine hydrochloride is a BCS class II anti-hypertensive drug with poor solubility and low bioavailability of about 10%. Solid dispersion preparation through solvent evaporation technique was proven to enhance the solubility and bioavailability of this drug. In the present study, C_{max} of the lercanidipine optimised solid dispersion 1715.317±1.45 ng/ml was significant ($p<0.05$) as compared to the pure drug suspension formulation 564.88±1.75 ng/ml. T_{max} of both optimised solid dispersion formulation and pure drug was 1.0±0.4 and 1.5±0.5 h, respectively. $AUC_{0-\infty}$ infinity for lercanidipine optimised solid dispersion formulation was higher (6190.64±1.42 ng.h/ml) than the pure drug suspension 2046.54±1.67 ng.h/ml. Statistically, AUC_{0-t} of the optimised solid dispersion formulation was significantly higher ($p<0.05$) as compared to pure drug suspension formulation. Higher amount of drug concentration in blood indicated better systemic absorption of lercanidipine from optimised solid dispersion formulation as compared to the drug suspension

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formulation. Thus, it can be concluded that Lercanidipine solid dispersions are one of the promising methods to increase its solubility and bioavailability.

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