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FORMULATION AND DEVELOPMENT OF SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEMS (SMEDDS) OF LERCANIDIPINE HCL

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Abstract

The present work was planned to design formulation and characterization of SMEDDS of Lercanidipine HCl. Lercanidipine HCL is long action dihydropyridine calcium channel blocker fer treatment of hypertension and chronic stable angina pectoris. To increase the solubility, oral absorption of crystalline lercanidipine HCl solvent evaporation technique is employed. To change its form. After X ray diffraction studies it is clear that crystalline form of lercanidipine HCl changes to substantially pure amorphous form. Thus, our study confirmed that the SMEDDS formulation can be used or a possible alternative to traditional oral formulations of lercanidipine HCl to improve its solubility and dissolution rate.

Introduction:

Oral route has been the major route of drug delivery for the chronic treatment of many disease. However, oral delivery of 50 % of the drug compounds is hampered because of high lipophilicity of drug itself. Nearly 40 % of new drug candidates exhibit low solubility in water[2].

SEDDS are easily manufactured and physically stable isotropic mixture of oil, surfactant and hydrophilic cosurfactant and solubilized drug substance that are suitable for oral delivery in soft and hard gelatin capsules. These formulations that rapidly and spontaneously form fine oil in water emulsions or microcmulsions upon dilution in water, owe their self emulsifying properties to a negative or low energy requirement for emulsion formulation. Thus self emulsifying formulations are readily, dispersed in the GI tract where the motility of stomach and small intestine, body movement provider the agitation necessary for emulsification. SEDDS produce opaque, white emulsion with lipid droplet sizes of approximately 100 nm[7]

Plan of Work

The present work was planned to design formulation and characterization of SMEDDS of Lercanidipine HCl.

This study divided in to the following parts

1. Analytical method development

a. Determination of λ max of Lercanidipine HCl.

b. Construction of standard calibration graph by using UV Spectrophotometer.

2. Formulation and development (SMEDDS) of Lercanidipine HCl

Selection of components of microemulsion

a. Compatability of excipients with hard gelatin capsule shell.

b. Solubility studies of Crystalline Lercanidipine HCl in different excipients and oils.

c. Solubility enhancement of Crystalline Lercanidipine HCl by solvent evaporation method.

   1. Preparation of Amorphous Lercanidipine from Crystalline Lercanidipine.

   2. X-ray diffraction studies.

d. Determination microemulsion existence region.

e. Formulation of SMEDDS of amorphous Lercanidipine HCl.

f. Characterization of (SMEDDS) of Lercanidipine HCl.

g. Evaluation of SMEDDS of Lercanidipine HCl.

   1. In vitro dissolution of SMEDDS for Drug Release.

   2. Drug Content estimation.

Materials and Methods

Table 1: List of Materials.

S. No	Name of Materials used	Supplier
1	Capmul MCM	ABITEC Co Ltd, Janesville
2	Tween 80	Seppic france
3	Lercanidipine HCl	Glenmark API Ankleswar
4	Methanol	Ranchem
5	Dichloromethane	Ranchem
6	Gelucire 44/14	Gattefose france
7	Imwitor 380	Sassol
8	Captex 100	Abitec Co.Ltd Janesville

9	Captex 200	Abitec Co.Ltd Janesville
10	Captex 300	Abitec Co.Ltd Janesville
11	Lauroglycol 90	Gattefose france
12	Plurol olequeie	Sassol
13	Miglyol 810N	Sassol
14	Labrafil M 1944s	Gattefose france
15	Capryol 90	Gattefose france
16	Sesame oil	Croda Chemicals
17	Peanut oil	Croda Chemicals
18	Castor oil	Croda Chemicals
19	Olive oil	Croda Chemicals
20	Soyabean oil	Croda Chemicals
21	Conconut oil	Croda Chemicals
22	Peceol	Croda Chemicals
23	Olive oil	Croda Chemicals
24	Safflower oil	Croda Chemicals

List of Instrument and Equipments

Table 2: List of Instrument & Equipments

S. No	Name of Materials used	Supplier
1	UV-VIS spectrophotometer	Shimidzu UV 1601. Perkin elmer
2	USP II Dissolution Apparatus	Electrolab
3	Rotavapor	BUCHI Switzerland
4	X ray diffractometer	X'pert Pro Panalytical
5	Particle size Analyser	Beckman coulter N4 plus
6	pH meter	Labendia

7	Thermometer	Colour con
8	Magnetic stirrer	Remi Equipment Pvt. Ltd.
9	Centrfugation	Remi Motors Pvt. Ltd.
10	Ultrasonicator	Sonic Moters

Drug Profile [5,6,15,16]

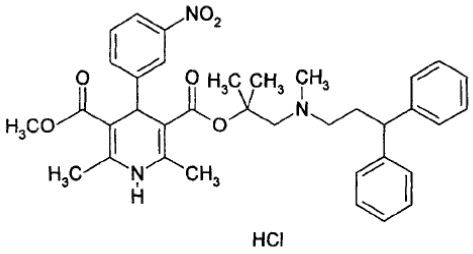
Lercandipine HCL: Lercanidipine HCL is long action dihydropyridine calcium channel blocker fer treatment of hypertension and chronic stable angina pectoris.

Generic name – lercanidipine

Chemical name – methyl [2-(3,3 – diphenyl propyl – methyl – amino) 1,1- dimethyl- ethyl) 2,6 – dimethyl 4-(3-nitrophenyl) – 1,4- dihydropyridine – 3, 5- dicarpoxylate

Chemical formula: $C_{36}\ H_{41}\ N_3\ O_6$.

Chemical structure:



Drug category	**:**	Antihypertensive Drug
Molecular formula	**:**	$C_{33}\ H_{34}\ FN_2\ O_5$
Molecular weight	:	648.205g/mol
Physical state	:	Citrine yellow crystalline solid powder
Oral Bioavailability	:	44%
Plasma protein binding	:	76% - 99%
Volume of Distrubution	:	2-2.5 L/Kg
Clearance	:	11-14.5 L / hr. Kg
Half life	:	2.7-4.6 hr
Time of maximum concentration	:	1.2 – 3.3.hr

Routes of administration : oral

Dose : Adult -10 mg once daily before food increase after 2 weeks to 20 mg daily if necessary

Solubility Water : 9.3mg / 100ml

Methanol 95%- 4.7g / 100ml

Methanol 99% - 4.7g / 100ml

Dimethyl formamide:>100g/100-ml

Partition coefficient (log P) : 6.1

Apparent Dissociation Constant : 6.8

Pharmacology

Lercanidipine, a dihydropyridine calcium- channel blocker, is used alone or with an angiotensin- converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and prinzmetal's variant angina., lercanidipine is similar to other peripheral vasodilators.

Lercanidipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes possibly by deforming the channel, inhibiting ion-control gating mechanisms, and / or interfering with the release of calcium from the sarcoplasmic reticulum.

Mechanism of Action

Lercanidipine is a dihydropyridine calcium channel blocker which acts by inhibiting the inward through displacement of calcium ions through slow channels vascular smooth muscles and myocardium during depolarization, its main effect is vasodilation because it has greater selectivity for vascular smooth muscles.

Adverse reaction

Tachycardia, oedema, flushing, headache, dizziness, asthenia, rash, diarrhoea, polyuria, palpitations, hypotension, drowsiness, myalgia.

Clinical indication

For the treatment of hypertension and management of angina pectoris and Raynaud's syndrome.

Preparation of standard calibration curve in Methanol

10 mg of drug was weighed accurately and dissolved in methanol in volumetric flask. The volume was made up to 100ml with methanol to obtain stock solution of concentration 100 μg/ml. This solution was then serially diluted to

methanol to give solutions of concentration ranging from 5 μg/ml to 50 μg/ml the absorbance was read at 355 nm using suitable blank on Perkin Elmer UV visible spectrophotometer and standard calibration curve was plotted.

Table-3: Standard curve in Methanol.

S.No.	Concentration (μ g/ml)	Absorbance
1	0	0
2	5	0.0517
3	10	0.1083
4	15	0.1547
5	20	0.2080
6	25	0.2586
7	30	0.3032
8	35	0.3572
9	40	0.4135
10	45	0.4652
11	50	0.5113

Results and Discussion

One important consideration when formulating a self emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen in vivo, therefore the components used in the system could have high solubilization capacity for the drug, ensuring the solubilization of the drug in resultant dispersion. Out of different excipients screening for crystalline Lercanidipine HCl solubilization. Capmul MCM and Tween 80 are most promising excipients. Capmul MCM show the highest solubility (around 15mg/g) while Tween 80 accomodated approximately (8mg/gm) of crystalline Lercanidipine HCl. Self –microemulsifying systems from fine oil –water emulsions with only gentle agitation upon their introduction agitation upon their introduction in to aqueous media. Surfantant get preferentially absorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of micro emulsion formulation. Therefore, the selection of oil and surfactant, play an important role in formation of the microemulsion. To obtain the balance between solubility and micro emulsion quality, both these

excipients were mixed in (1:9, 2:8, 3:7 ….. 9:1). Like that 11 ratios are prepared. Capmul MCM used as oil phase (Solubilizer) and Tween 80 act as surfactant in the system. ternary phase diagram with and without drug are constructed to determine the region of microemulsion formation. (9:1) ratio was selected for the formulation of SMEDDS, because of it higher solubilization accomodation capacity for crystalline lercanidipine HCl. To increase the solubility, oral absorption of crystalline lercanidipine HCl solvent evaporation technique is employed. To change its form. After X ray diffraction studies it is clear that crystalline form of lercanidipine HCl changes to substantially pure amorphous form. Which have found the higher solubility in same excipients (Capmul MCM, Tween 80) as compare to crystalline lercanidipine HCl. Capmul MCM show highest solubility (around 80 mg/g) while Tween 80 accomodated approximately (50 mg/gm) of Amorphous lercanidipine HCl. That means 5 times increase in solubility is occur. Ternary phase diagrams were plotted at the ratio (1:9, 2:8, 3:7 …… 9:1) like that 11 ratios were prepared, 9:1 ratio was selected for the formulation of SMEDDS of amorphous lercanidipine HCl because of its highest solubilization capacity and no chance of precipitation. Both the formulations are clear, transperant, and low viscous. In the present study both Capmul MCM and Tween 80 were tested for phase behavior studies. As seen the ternary plot. Tween 80 and Capmul MCM gave a wider micro emulsion region. Thus Tween 80 and Capmul MCM was selected as the preferred vehicle for the optimized formulation. Both the formulations of SMEDDS subjected to physical stability like freeze thawing, centrifugation, particle size analysis, P^H determination. After this studies both formulation found to be clear, transparent, low viscous isotropic solution with good stability. The in vitro dissolution and Drug content studies were carried out. Drug release from the SMEDDS formulations was found to be significantly higher as compared with that of plain lercanidipine HCl (reference capsules). It could be suggested that the SMEDDS formulation resulted in spontaneous formation of microemulsion with small droplet size. Which permitted a faster rate of drug release in to aqueous phase, much faster than that of plain lercanidipine HCl (reference Capsules), thus this greater availability of dissolved lercanidipine HCl from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability.

Formulation and Development of SMEDDS of Lercanidipine HCl

Selection of components of microemulsion (SMEDDS)

Compatibility of excipients with hard gelatin shell: Excipients are selected according there compatibility with hard gelatin shell and solubilizing capacity for Lercanidipine HCl. According to preliminary studies conducted. Tween 80 and capmul MCM are most promising excipients for the formulation of SMEDDS result given in the table 5.

Preparation of Amorphous Lercanidipine HCl from crystalline Lercanidipine HCl was solvent evaporation method

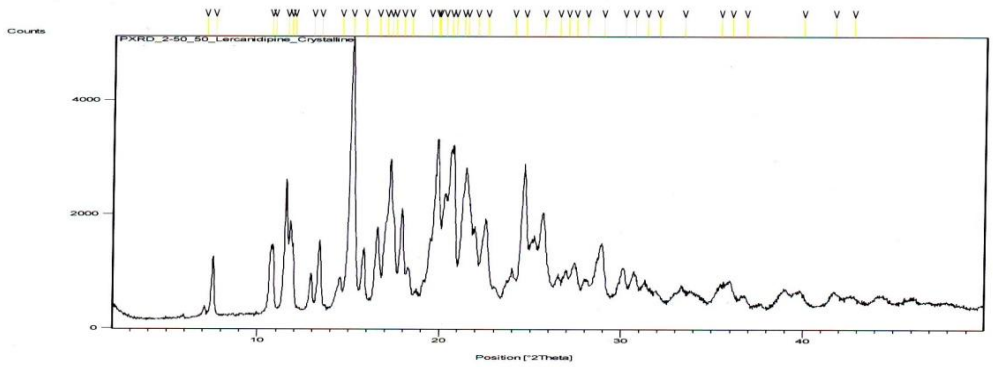
Amorphous Lercanidipine HCl was prepared from Crystalline Lercanidipine HCl by solvent evaporation method by using Dichloromethane. The solubility of the amorphous Lecranidipine HCl was compared to solubility of crystalline Lecranidipine HCl. After solvent evaporation we get the substanitially pure amorphous Lecranidipine HCl, which has 5 times greater aqueous solubility and greater solubility in Tween 80 and Capmul MCM as compare to crystalline Lecranidipine HCl. So the conversion of crystal form to amorphous form of Lercanidipine showed the enhancement of solubility. Result are given in table no8.

Solubility of Crystalline Lecranidipine HCl and Amorphous Lercanidipine HCl

S.No	Excipients	Solubility of Crystalline Lercanidipine HCl	Solubility of Amorphous Lercanidipine HCl
2	Tween 80	8 mg/gm	50 mg/gm
3	Capmul MCM	15 mg/gm	80 mg/gm

X ray Diffraction Studies of Crystalline Lercanidipine HCl and Amorphous Lercanidipine HCl

X ray diffraction studies indicates the difference between the physical state and crystal structure of particles of crystalline Lercanidipine HCl and amorphous Lercanidipine HCl. After solvent evaporation of crystalline Lercanidipine HCl there is changes occur in the physical state of drug. After the X ray diffraction studies it was proved that crystalline form of Lercanidipine HCl was changed to Amorphous form. Fig 7 and Fig 8 shows the comparison between crystalline Lercanidipine HCl and Amorphous Lercanidipine HCl.



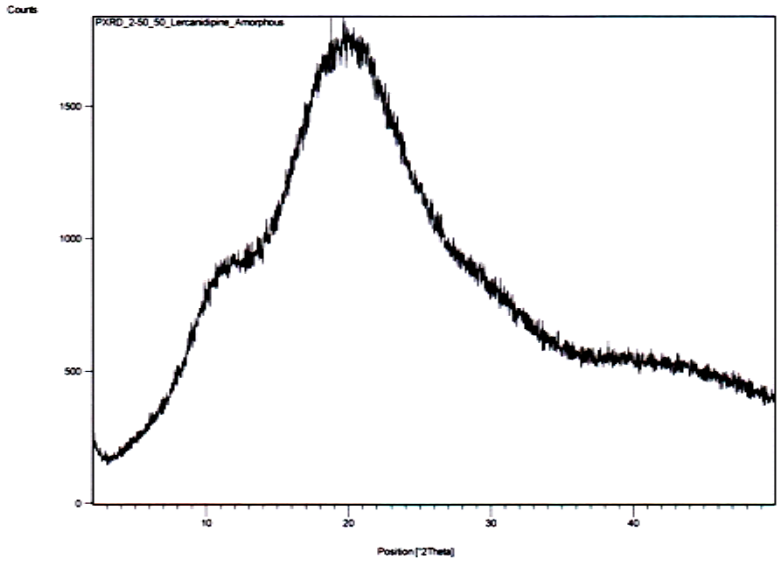
Peak List:

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Height [cts]	Area [cts*°2Th.]
7.0852	12.47652	4.26	198.85	19.69
7.5609	11.69267	21.38	998.96	115.39
10.6847	8.28014	22.64	1057.78	104.73
10.8398	8.16206	24.05	1123.79	111.26
11.5504	7.66142	49.38	2307.47	266.53
11.7746	7.51603	34.03	1590.03	157.43
11.9335	7.41631	22.77	1064.14	70.24
12.9714	6.82516	11.84	553.09	54.76
13.4116	6.60212	25.69	1200.36	217.88
14.5486	6.08860	10.08	470.80	69.92
15.1376	5.85299	100.00	4672.90	1002.42
15.8176	5.60288	19.46	909.52	135.07
16.5788	5.34730	27.96	1306.49	258.71
16.9804	5.22172	26.20	1224.46	161.64
17.2737	5.13373	52.85	2469.46	326.00
17.4930	5.06986	27.59	1289.17	106.37
17.8969	4.95633	34.23	1599.64	237.57
18.3285	4.84057	10.04	469.21	85.17
19.4380	4.56671	19.47	909.64	105.07
19.8141	4.47718	59.11	2762.10	225.39

Glenmark Pharmaceuticals Ltd

19.8978	4.46222	57.00	2663.64	175.81
20.2655	4.38207	38.33	1790.92	236.42
20.5766	4.31652	53.49	2499.48	247.47
20.7985	4.27098	48.22	2253.29	334.64
21.2228	4.18653	33.47	1563.94	154.84
21.4449	4.14368	47.62	2225.37	367.22
21.9653	4.04666	24.35	1137.71	187.74
22.5568	3.94187	28.44	1328.92	263.15
23.9974	3.70839	10.35	483.50	63.83
24.6420	3.61284	49.70	2322.58	421.58
25.6622	3.47148	31.26	1460.76	168.73
26.5064	3.36279	7.69	359.55	71.20
26.9427	3.30933	9.57	447.00	59.01
27.4030	3.25477	12.36	577.80	152.55
28.0251	3.18392	6.08	284.03	56.24
28.9315	3.08620	19.32	902.57	119.15
30.1046	2.96856	11.32	528.85	104.72
30.6524	2.91675	9.91	463.00	91.68
31.2860	2.85911	6.84	319.48	63.26
31.9548	2.80078	3.53	164.82	43.52
33.3281	2.68844	5.89	275.24	54.50
35.3483	2.53929	6.18	288.93	95.35
35.9851	2.49580	9.29	434.17	85.97
36.7722	2.44417	3.96	185.00	48.84
39.9020	2.25938	5.35	250.10	66.03
41.6570	2.16816	4.96	231.69	91.76
42.6916	2.11623	3.37	157.71	102.95

Fig 8 Amorphous Lercanidipine HCl shows a typically exhibit broad peaks



Peak List:

Determination of Microemulsion existence region

Construction Ternary phase diagram

Many researcher have studied the phase behaviour of the reported system namely by plotting pseudoternary phase diagrams. Pseudoternary pahse diagram are not very useful for self microemulsifying systems, it is not helping in deciding the concentration of oil, that should be used for self microemulsifying systems. Hence, need of hour is to modify phase diagrams such that they can give idea about the concentration of components to be used so as to achieve self emulsification.

Phase behaviour investigations of this systems demonstrated the suitable approach to determine the oil phase, surfactant concentration with which is the transparent low viscous microemulsion (SMEDDS) is formed and also phase diagram were constructed in the presence of Lercanidipine HCl (Drug). SMEDDS from fine solubilizer water emulsion with only gentle agitation, upon their introduction in to aqueous medium. Ternary phase diagram were constructed to identify the self – microemulsifying region to optimize the concentration of oil, solubilizer (Capmul MCM). Surfactant (Tween 80) and water it was observed that increased in the concentration surfactant (Tween 80) increase in spontaneity of self emulsifying region. Therefore SMEDDS formulation contain the optimum concentration of Tween 80. Therefore view point formulation of SMEDDS contents Tween 80 (90%) and capmul MCM (10%) i.e oil / surfactant ratio (9:1) was selected to their solubilization capacity towards the drug and water concentration was selected according how much water taken by formulation for spontaneous self emulsifying region.

Drug incorporating ternary phase diagram were prepared by dissolving the drug in the increasing order in different composition Capmul MCM / Tween 80. A ternary phase diagram of the investigated composition of Capmul MCM / Tween 80/ water is presented in fig 9 and drug incorporating ternary phase diagram of the investigated composition of capmul MCM / Tween 80 / water is presented in fig 10,11.

Ternary phase diagram (Placebo)

Table 9: Concentration of Tween 80 / Capmul MCM / water in Percentage

S.No	Tween 80	Capmul MCM	Water
1	58.53	0.0	41.17
2	54.21	6.12	39.75
3	50.01	12.52	37.5
4	43.76	18.76	37.5

5	39.52	26.32	34.21
6	36.24	36.24	27.53
7	32.37	48.45	19.35
8	25.06	58.40	16.66
9	17.31	68.98	13.79
10	8.77	78.94	12.28
11	0.0	87.75	12.28

Fig No : 9 Ternary Phase Diagram (Placebo) Tween 80

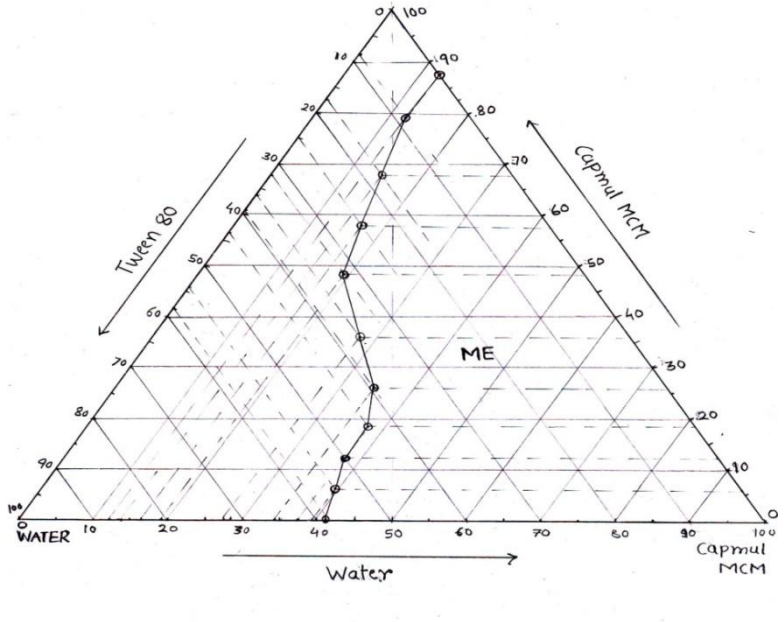


Table 10: Ternary phase diagram with Amorphous Lercanidipine HCl (100 mg).

S.No	Tween 80	Capmul MCM	Water	Drug
1	62.51	0.03	37.75	100 mg
2	56.26	6.26	37.5	100 mg
3	51.93	13.03	35.06	100 mg
4	50.73	21.76	27.53	100 mg
5	43.53	29.04	27.53	100 mg
6	36.24	36.28	27.53	100 mg
7	33.35	50.06	16.66	100 mg
8	25.93	60.36	13.79	100 mg
9	17.25	69.03	13.79	100 mg
10	8.78	79.0	12.28	100 mg
11	0.00	87.78	12.28	100 mg

Fig No: 10 Ternary Phase Diagram with Amorphous Lercanidipine (100 mg) Tween 80

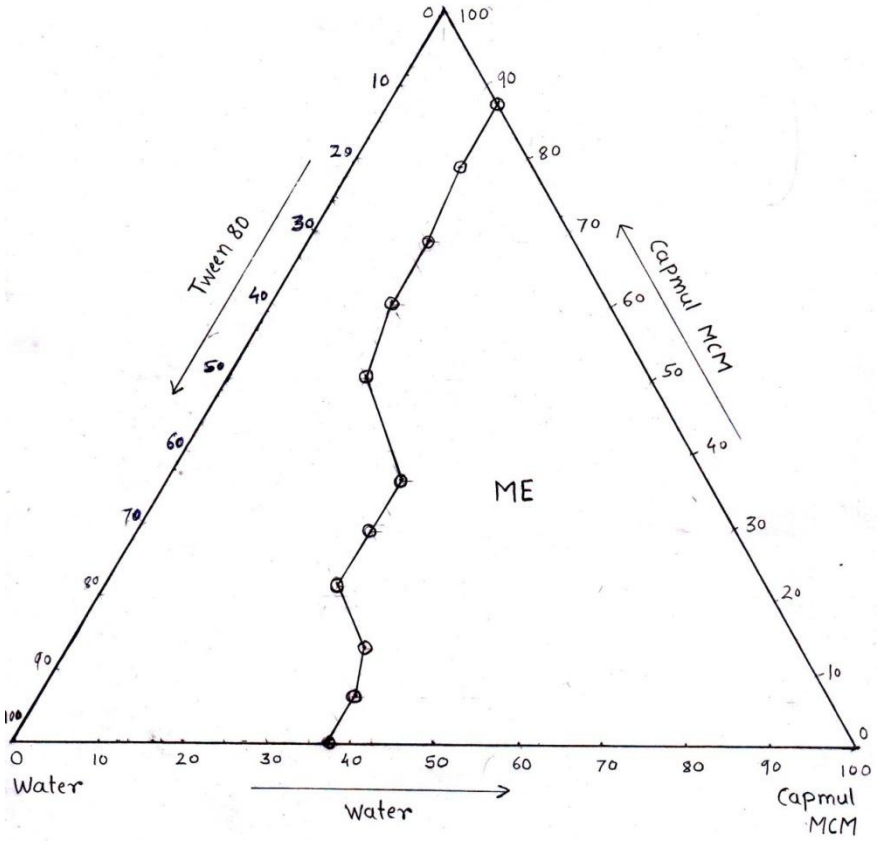
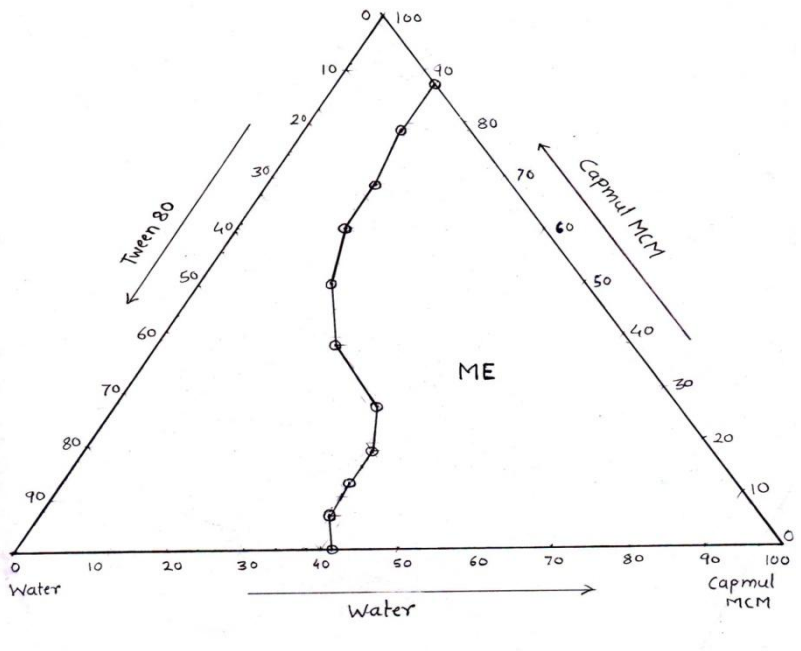


Table 11: Ternary phase diagram, with amorphous Lercanidipine HCl concentration of Tween 80 / Capmul MCM / water given in percentage

S.No	Tween 80	Capmul MCM	Water	Drug
1	58.83	0.00	41.17	250 mg
2	55.56	6.18	38.27	250 mg
3	50.02	12.55	37.5	250 mg
4	43.76	18.80	37.5	250 mg
5	39.47	26.36	34.21	250 mg
6	38.47	38.52	23.07	250 mg
7	33.35	50.06	16.66	250 mg
8	25.87	60.38	13.79	250 mg
9	17.31	68.98	13.79	250 mg
10	8.77	78.96	12.28	250 mg
11	0.0	87.71	12.28	250 mg

Fig No: 11Ternary Phase Diagram with Amorphous Lercanidipine (250 mg) Tween 80



9.4 Formulation of Amorphous Lercanidipine HCl (SMEDDS)

According to procedure formulations was prepared formula given in the table no.12.

Table 12: Formulation of SMEDDS (Amorphous).

Formula	% W/W	Quantity (gm)
Tween 80	510 g	5.10 g
Capmul MCM	60 g	0.60 g
Lercandipine HCl	30.11 g	0.31 g

9.5 Physical Characterization of SMEDDS

9.5.1 Freez Thawing and Centrifugation

Freez thawing employed to evaluate the stability of formulation SMEDDS is kept under stress condition 2-8^{0}C (Freezing) and 30 – 40^{0}C (thawing) for 24 hrs 2 – 8^{0}C and 30 – 40^{0}C (Freez thawing) respectively. Centrifugation also employed to evaluate the physical stability of SMEDDS centrifugation of three different samples of SMEDDS The results were given in table no 13 and 14 respectively.

In vitro dissolution of SMEDDS of Lercanidipine HCl for drug release

Dissolution of drug in aqueous medium is the rate limiting step for the absorption of poorly water soluble drugs. The dissolution of poorly water soluble drugs can be improved by increasing the solubility of the drug in the medium and ultimately in the GIT, therefore the dissolution study was performed for SMEDDS of Amorphous Lercanidipine HCl.

The Invitro drug release profile of Lercanidipine HCl in 0.1 N HCl (Media) from SMEDDS are given in table no 16, From developed SMEDDS was found to be significantly higher than plain drug (Lercanidipine HCl). However though the self microemulsifying formulation were able to disperse in about two minutes. An initial lag time of about five minutes was observed in the dissolution study. This could be attributed to time required for the disintegration of capsule shell and later to the passage of SMEDDS particles through the sinker.

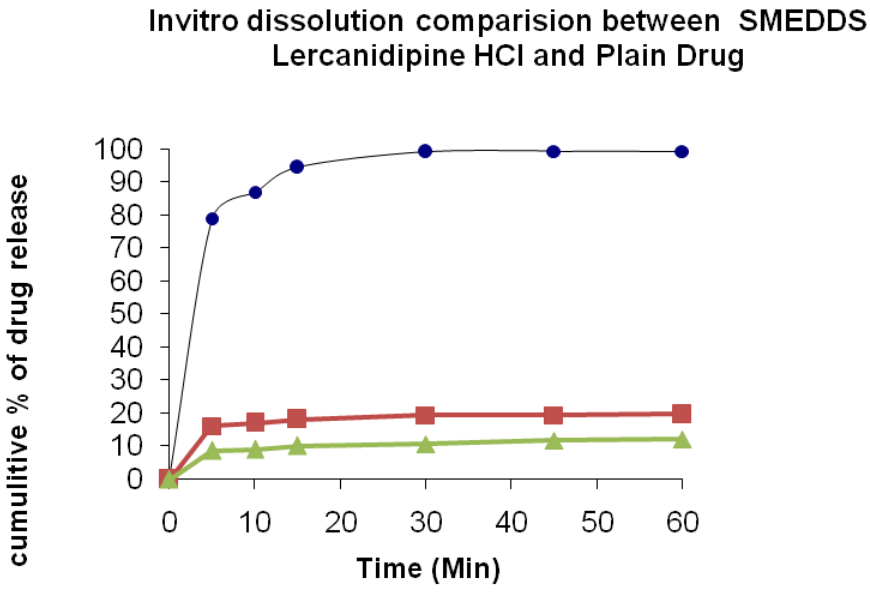
Formulations of SMEDDS is found to be released 99% in 30 min and reference capsule filled with crystalline Lercanidipine HCl and amorphous Lercanidipine HCl (plain drug) was found to be release only about 10% in 30 min and 19% in 30 min. The increase release rate of the drug from SMEDDS could be attributed to the

1. Mean particle size invariably less than 18 nm
2. Ability of vehicle to keep Lercanidipine HCl in solubilized state for sufficiently longer period

Table 16: Release Profile for SMEDDS of Amorphous Lercanidipine and Plain Drug

S.No.	Time	Cumulative % drug release of Amorphous lercanadipine form SMEDDS	Cumulative % drug release of Amorphous lercanadipine (Plain drug) from SMEDDS	Cumulative % drug release of Crystalline Lercanidipine (Plain drug) from SMEDDS
1	0	0	0	0
2	5	79	16.24	8.7
3	10	87.08	17.12	9.10
4	15	94.52	18.23	10.1
5	30	99.23	19.48	10.71
6	45	99.52	19.52	11.84
7	60	99.52	19.74	12.18

Fig No: 12



In vitro dissolution drug release comparision between SMEDDS and plain drug given in fig no: 12.

9.7 Drug Content estimation

Table: 17 Drug content of the optimized formulation.

Formulation	Assay (Mg/capule)
SMEDDS of Amorphous lercanidipine HCl	19.80 (99.00%)

From the above table 17 it can be seen that assay of formulation comes between 98-100%.

Conclusion

An optimized SMEDDS formulation of Lercanidipine HCl with Tween 80, Capmul MCM, was successfully developed. The SMEDDS formulation showed increased solubility and increased dissolution rate and so there could be an increase in the oral bioavailability poorly water soluble drug, Lercanidipine HCl.

This will have significant implications in future dosage development for poorly water- soluble drugs, such as lercanidipine HCl in using self microemulsifying drug delivery system (SMEDDS)

Thus, our study confirmed that the SMEDDS formulation can be used or a possible alternative to traditional oral formulations of lercanidipine HCl to improve its solubility and dissolution rate.

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