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D-Optimal Design Based Statistical Optimization of Liquisolid Compacts of Lercanidipine Hcl for Enhancement of Solubility

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KEYWORDS

ABSTRACT:

In the current investigation, it was aimed to develop, evaluate and statistically optimize the liquisolid compacts of poorly soluble drug, lercanidipine HCl for the enhancement of their solubility. The selected drug come under BCS class-II which have low solubility and high permeability. Bioavailability of lercanidipine HCl is 10% . Hence, it was proposed to improve their solubility and dissolution rate in turn to have improved bioavailability. Preformulation studies were conducted to identify the drug characteristics and to screen the suitable excipients for the formulations. Based on the number of factors and their levels proposed in the study, D-optimal design was used for optimization of liquisolid compacts of lercanidipine HCl. UV-Visible spectrophotometric methods were used for the estimation of drug in in-vitro studies. For liquisolid compacts formulation, Tween 80 and PEG 600 were selected as non-volatile solvents; Avicel, Fujicalin and Neusilin were selected as carriers whereas Aerosil and Kollidon were used as coating materials.

Micromeritic properties, assay, solubility and in-vitro dissolution studies were performed all the prepared formulations. Characterization studies were performed by FT-IR and DSC to study the compatibility of drug and excipients. Statistical optimization was done using Design Expert software version 12 by following numerical and graphical optimization techniques. Predicted formula was experimentally formulated and evaluated in triplicated and relative error determined. Selected optimized formulations were used for stability studies as per ICH guidelines at 25±2°C/60±5% RH for long term conditions and 40±2°C/75±5% RH under accelerated conditions for at least 6 months. The studies reveal that the development of liquisolid compacts is a versatile process to attain the proposed target of enhancement of solubility and dissolution rate. Hence, it was concluded that the development of liquisolid compacts of lercanidipine HCl addresses the solubility problem of the drug. Scale up of the proposed methods is also industrially possible and can be explored further to proceed for commercial industrial application.

Introduction

The performance of any drug depends on its availability at the site of action. For the drug to reach the site of action from the site of administration, it has to cross several physiological barriers. Two major factors that influence the movement of a drug across those barriers include solubility and permeability. Hence, a biopharmaceutics classification (BCS) index has been coined by the scientists to understand the nature of drug and thereby to conduct research to develop a suitable dosage form and preferred route of administration. Researchers also investigate the possibilities to improve those properties as desired for the better therapeutic action. Dealing with BCS class II drugs having poor solubility and high permeability is a challenging task for the researchers to utilize the drugs to their fullest potential.

In the current investigation, two drugs of BCS class II, namely lercanidipine HCl was selected to improve their solubility and thereby bioavailability. Lercanidipine HCl is the BCS class-II antihypertensive drug with only 10% bioavailability due to its first pass metabolism. It belongs to dihydropyridine type of calicium channel blocker. It reduces the increased blood pressure by causing vasodilatation.[1]

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Hypertension is one of the most important causes of premature death worldwide and the problem is growing in 2025, an estimated 1.56 billion adults will be living with hypertension. Hypertension is considered the third most important risk factor for disease burden in South Asia (2010). Hypertension poses a significant public health burden on India's cardiovascular health and healthcare system, with 57% of all stroke deaths and 24% of all coronary heart disease deaths in India directly attributable to hypertension. This is the cause. The World Health Organization ranks high blood pressure as one of the leading causes of premature death worldwide. The Global and Regional Burden of Disease and Risk Factors Survey (2001) systematically analysed population health data on causes of death and burden of disease and found that in South Asia, hypertension ranks second only to low birth weight and age. The pharmaceutical industry has embraced the Quality by Design (QbD) concept from the new ICH guidance, ICH Q8 (R2), to ensure efficient regulatory approval and effective product development. A deep understanding of QbD principles and the tools for establishing a QbD strategy are crucial in developing a successful product development strategy. By incorporating the QbD approach, pharmaceutical product development has achieved a high success rate in regulatory approvals and the development of stable formulations. Multivariate statistics and experimental designs are key components of QbD[2].

The concept of using statistical analysis during the planning stages of research, rather than after experimentation, was introduced by Sir Ronald Fisher in the early twentieth century. However, the pharmaceutical industry was slow to adopt these designs, relying on One Factor at a Time (OFAT) studies instead of implementing Quality by Design (QbD). This approach led to time-consuming procedures and unreliable results, resulting in difficulties in obtaining regulatory approvals. Commonly used tools in QbD include risk assessment, design of experiments (DoE), and process analytical technology (PAT). Design of Experiment (DoE) is a structured and organized method for determining the relationship between factors affecting a process and the process's output. It is an excellent tool for QbD, enabling scientists to systematically manipulate factors based on a pre-specified design. DoE involves planning experiments in advance, selecting process variables (factors) and responses, and choosing appropriate factors and their levels. The experimental design aims to maximize the amount of information that can be obtained for a given amount of experimental effort[3].

The mixture design statistical method is the most suitable method used in the optimizing the formulations when they have contain mixture of components i.e., excipients along with drug. There are many types of mixture designs, simple lattice design, simplex-centroid design, axial design and i-optimal design and D-optimal mixture design and in the current study, D-optimal design is used. D-optimal design minimizes the overall variance of the predicted regression coefficient by maximizing the value of determinant of the information matrix. The experimental region with D-optimal is not simplex but it is irregular and has a smaller number of runs compared to other designs and combined mixture and process variables can be used in the same experimental design[4].

METHODOLOGY:

Selection of non-volatile solvent [5]

Solubility of lercanidipine HCl was determined in propylene plycol, PEG 200, PEG 400, PEG 600 and Tween 80 to select non-volatile solvent. An excess amount of lercanidipine HCl was added to 10 ml of solvents in the small screw capped vial to prepare saturated solution. Sealed vials containing saturated solution of lercanidipine HCl were subjected to constant shaking on orbital shaker for 48 h at room temperature. After shaking, content of vials was centrifuged at 3000 rpm and supernatant was filtered through 0.45 µ cellulose acetate filter. Amount of drug in filtrate was measured using UV-Visible spectrophotometer at 240 nm after diluting with distilled water. The measurements were done in triplicate.

Preparation of liquisolid compacts of lercanidipine HCl [6]

Liquisolid compacts of lercanidipine HCl were prepared by using non-volatile solvents (Tween 80 and PEG 600), carriers (Avicel, Fujicalin and Neusilin), coating materials (Aerosil and Kollidon), and super disintegrant (sodium starch glycolate). The optimization of formulation was done following design of experiments as a part of Quality by Design (QbD).

Experimental design

The mixture design statistical method is the most suitable method used in the optimizing the formulations when they have contain mixture of components i.e.,

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excipients along with drug. There are many types of mixture designs, simple lattice design, simplex-centroid design, axial design and i-optimal design and D-optimal mixture design and in the current study, D-optimal design is used. D-optimal design minimizes the overall variance of the predicted regression coefficient by maximizing the value of determinant of the information matrix. The experimental region with D-optimal is not simplex but it is irregular and has a smaller number of runs compared to other designs and combined mixture and process variables can be used in the same experimental design. The selected independent variables with their levels are shown in **Table 1**. The proposed responses and their constraints are shown in **Table 2**.

Table 1: Independent variable codes used in the D-optimal experimental design for liquisolid compacts of lercanidipine HCl

Independent Variable	**Level**		
	Low (-1)	**Medium (**0)	**High (1**)
X1= Non-volatile solvent	Tween 80	-	PEG 400
X2= Carrier	Avicel	Fujicalin	Neusilin
X_3= Coating material	Aerosil	Kollidon	Without

Table 2: Dependent variables and their constraints for liquisolid compacts of lercanidipine HCl

Dependent Variable (Response)	**Constraint**
Y1= Carr's Index	Maximum
Y2= Solubility	Minimum
Y3= T30 (% drug released at 30 min)	Maximum

Design Expert software v12 was used for this study, to obtain critical values for achieving the desired response and the possible interaction effects of selected independent variables on responses. The D-optimal experimental design suggested 22 experiments for 3 independent factors at respective levels as shown in **Table 3**. Decoded and experimental working formula are shown in **Table 4** and 5 respectively. Liquid load factor (Lf) and carrier: coating material ratio (R) are shown in **Table 6**. Schematic representation of design and development of liquisolid compacts of lercanidipine HCl is shown in **Fig. 1.**

Table 3: Experimental design codes of independent variables as per D-optimal design for 3 factors at respective levels

Formulation Code	**Level of variable**		
	Non-volatile solvent (**X1**)	Carrier (**X2**)	Coating material (**X3**)
LLS1	-1	-1	-1
LLS2	-1	-1	0
LLS3	-1	-1	1
LLS4	1	-1	-1
LLS5	1	-1	0
LLS6	1	-1	1
LLS7	-1	0	-1
LLS8	-1	0	0
LLS9	-1	0	1
LLS10	1	0	-1
LLS11	1	0	0
LLS12	1	0	1

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LLS13	-1	1	-1
LLS14	-1	1	0
LLS15	-1	1	1
LLS16	1	1	-1
LLS17	1	1	0
LLS18	1	1	1
LLS19	-1	-1	0
LLS20	1	-1	1
LLS21	1	0	-1
LLS22	-1	1	1

Table 4: Decoded formulae for preparation of liquisolid compacts of lercanidipine HCl as per D-optimal design

Formulation code	Non-volatile solvent (X1)	Carrier (X2)	Coating material (X3)
LLS1	TWEEN 80	Avicel	Aerosil
LLS2	TWEEN 80	Avicel	Kollidon
LLS3	TWEEN 80	Avicel	Without
LLS4	PEG 600	Avicel	Aerosil
LLS5	PEG 600	Avicel	Kollidon
LLS6	PEG 600	Avicel	Without
LLS7	TWEEN 80	Fujicalin	Aerosil
LLS8	TWEEN 80	Fujicalin	Kollidon
LLS9	TWEEN 80	Fujicalin	Without
LLS10	PEG 600	Fujicalin	Aerosil
LLS11	PEG 600	Fujicalin	Kollidon
LLS12	PEG 600	Fujicalin	Without
LLS13	TWEEN 80	Neusilin	Aerosil
LLS14	TWEEN 80	Neusilin	Kollidon
LLS15	TWEEN 80	Neusilin	Without
LLS16	PEG 600	Neusilin	Aerosil
LLS17	PEG 600	Neusilin	Kollidon
LLS18	PEG 600	Neusilin	Without
LLS19	TWEEN 80	Avicel	Kollidon
LLS20	PEG 600	Avicel	Without
LLS21	PEG 600	Fujicalin	Aerosil
LLS22	TWEEN 80	Neusilin	Without

Table 5: Experimental working formula for preparation of liquisolid compacts of lercanidipine HCl as per D-optimal design

Formulation Code	Liquid Medication (W)			X_2= Carrier (Q)			X_3= Coating Material (q)		Disintegrant	Total Weight (gm) (10 Doses)
	LER	X_1= Non-Volatile Solvent								
		TWE	PEG	AVI	FUJ	NEU	AER	KOL	SSG	
LLS1	0.10	0.84	0.00	3.00	0.00	0.00	0.15	0	0.205	**4.295**
LLS2	0.10	0.84	0.00	3.00	0.00	0.00	0.00	0.15	0.205	**4.295**
LLS3	0.10	0.84	0.00	3.00	0.00	0.00	0.00	0	0.197	**4.137**
LLS4	0.10	0.00	0.40	1.50	0.00	0.00	0.15	0	0.108	**2.258**

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LLS5	0.10	0.00	0.40	1.50	0.00	0.00	0.00	0.15	0.108	**2.258**
LLS6	0.10	0.00	0.40	1.50	0.00	0.00	0.00	0	0.100	**2.100**
LLS7	0.10	0.84	0.00	0.00	3.00	0.00	0.15	0	0.205	**4.295**
LLS8	0.10	0.84	0.00	0.00	3.00	0.00	0.00	0.15	0.205	**4.295**
LLS9	0.10	0.84	0.00	0.00	3.00	0.00	0.00	0	0.197	**4.137**
LLS10	0.10	0.00	0.40	0.00	1.50	0.00	0.15	0	0.108	**2.258**
LLS11	0.10	0.00	0.40	0.00	1.50	0.00	0.00	0.15	0.108	**2.258**
LLS12	0.10	0.00	0.40	0.00	1.50	0.00	0.00	0	0.100	**2.100**
LLS13	0.10	0.84	0.00	0.00	0.00	3.00	0.15	0	0.205	**4.295**
LLS14	0.10	0.84	0.00	0.00	0.00	3.00	0.00	0.15	0.205	**4.295**
LLS15	0.10	0.84	0.00	0.00	0.00	3.00	0.00	0	0.197	**4.137**
LLS16	0.10	0.00	0.40	0.00	0.00	1.50	0.15	0	0.108	**2.258**
LLS17	0.10	0.00	0.40	0.00	0.00	1.50	0.00	0.15	0.108	**2.258**
LLS18	0.10	0.00	0.40	0.00	0.00	1.50	0.00	0	0.100	**2.100**
LLS19	0.10	0.84	0.00	3.00	0.00	0.00	0.00	0.15	0.205	**4.295**
LLS20	0.10	0.00	0.40	1.50	0.00	0.00	0.00	0	0.100	**2.100**
LLS21	0.10	0.00	0.40	0.00	1.50	0.00	0.15	0	0.108	**2.258**
LLS22	0.10	0.84	0.00	0.00	0.00	3.00	0.00	0	0.197	**4.137**

LER-Lercanidipine HCl; TWE- Tween 80; PEG- Polyethylene Glycol 600; MCC - Avicel pH 101; FUJ- Fujicalin; NEU-Neusilin; AER - Aerosil 200; KOL – Kollidon; SSG- Sodiumstarchglycolate;

Table 6: Liquid load factor (Lf) and carrier: coating material ratio (R) for preparation of liquisolid compacts of lercanidipine HCl as per D-optimal design

Formulation code	Unit dose (mg)	Liquid medication (W)	Carrier (Q)	Coating material (q)	LF=W/Q	R=Q/q
LLS1	0.429	0.94	3.00	0.15	0.313	20.0
LLS2	0.429	0.94	3.00	0.15	0.313	20.0
LLS3	0.414	0.94	3.00	0.00	0.313	0.0
LLS4	0.226	0.50	1.50	0.15	0.333	10.0
LLS5	0.226	0.50	1.50	0.15	0.333	10.0
LLS6	0.210	0.50	1.50	0.00	0.333	0.0
LLS7	0.429	0.94	3.00	0.15	0.313	20.0
LLS8	0.429	0.94	3.00	0.15	0.313	20.0
LLS9	0.414	0.94	3.00	0.00	0.313	0.0
LLS10	0.226	0.50	1.50	0.15	0.333	10.0
LLS11	0.226	0.50	1.50	0.15	0.333	10.0
LLS12	0.210	0.50	1.50	0.00	0.333	0.0
LLS13	0.429	0.94	3.00	0.15	0.313	20.0
LLS14	0.429	0.94	3.00	0.15	0.313	20.0
LLS15	0.414	0.94	3.00	0.00	0.313	0.0
LLS16	0.226	0.50	1.50	0.15	0.333	10.0
LLS17	0.226	0.50	1.50	0.15	0.333	10.0
LLS18	0.210	0.50	1.50	0.00	0.333	0.0
LLS19	0.429	0.94	3.00	0.15	0.313	20.0
LLS20	0.210	0.50	1.50	0.00	0.333	0.0
LLS21	0.226	0.50	1.50	0.15	0.333	10.0
LLS22	0.414	0.94	3.00	0.00	0.313	0.0

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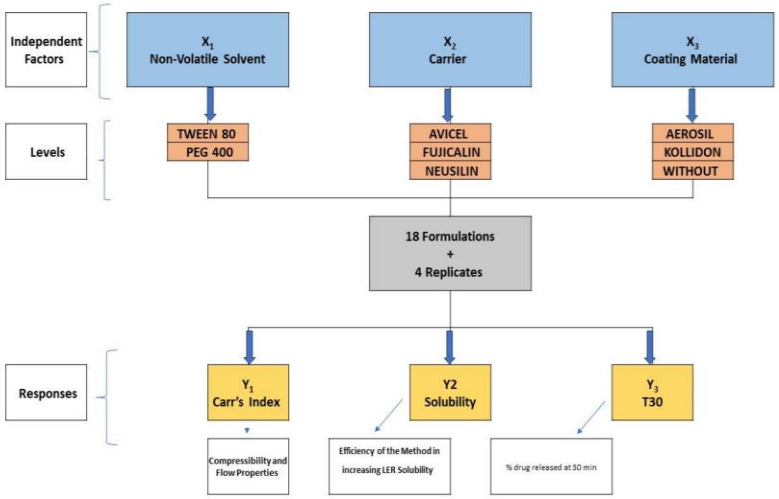


Fig. 1: Schematic representation of design and development of liquisolid compacts of lercanidipine HCl

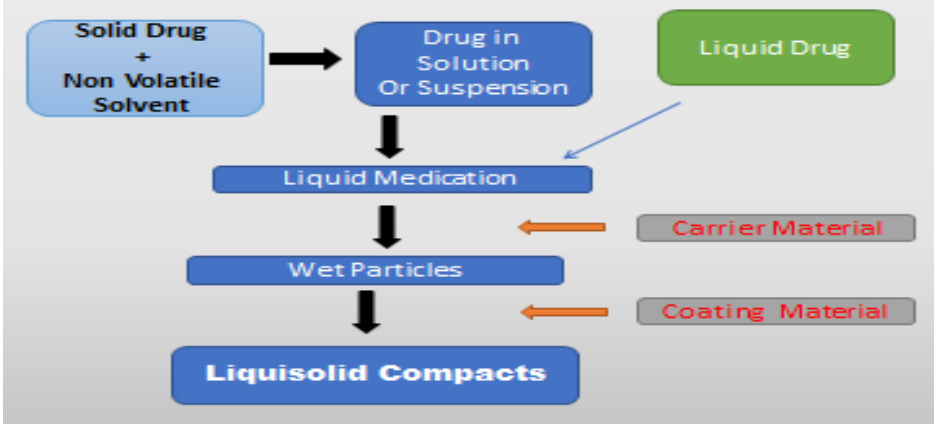
Preparation of liquisolid compacts of lercanidipine HCl following D-optimal design [7]

Desired quantities of previously weighed solid drug and the liquid vehicle were taken in a beaker and heated to 80-90°C with constant stirring, until a homogenous drug solution was obtained. The mixing procedure then conducted in three stages:

In the first stage, weighed quantity of carrier material blended with liquid medication in order to evenly distribute the liquid medication into the powder.

In the second mixing stage, calculated quantities of coating material were added to the system and blended for 2 min. The liquid powder admixture then left undisturbed for approximately 5 min to allow the drug solution to be absorbed into the interior of the powder particles.

In the third stage, the powders blend with a calculated quantity of super disintegrant (5%) for another 30 sec producing the final liquisolid formulation.



Evaluation of liquisolid compacts of Lercanidipine HCl

Micromeritic properties of formulation, percentage practical yield, drug content estimation, solubility studies and in-vitro dissolution studies were performed as per the procedures discussed in section 4.3.

Statistical optimization of liquisolid compacts of lercanidipine HCl [8]

To optimize all the responses with different targets, multi-criteria decision approaches such as a numerical optimization technique and graphical optimization technique were used. The optimized formulation was obtained by applying constraints on dependent variable responses.

Predicted formulation was selected based on the criteria to attain the maximum solubility, minimum Carr's

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Index and maximum drug released at 30 min. Various feasibility and grid searches were executed to establish the optimum formulation. The recommended concentrations of the independent variables were calculated by the Design Expert 12 software from the above techniques which indicated the highest desirability close to 1.0. Triplicate experimental studies were performed as per the predicted formula and the relative error estimated.

Characterization of liquisolid compacts of lercanidipine HCl [9]

As a part of characterization analysis, FT-IR, and DSC studies were performed for the optimized formulation and compared with the pure drug spectra/scan to understand the influence of excipients on drug as discussed in section 4.5.

Results and discussion

Selection of non-volatile solvents for the formulation of liquisolid compacts[7]

Solubility of lercanidipine HCl in different non-volatile solvents was determined and the results are shown in **Table 7** and graphical presentation is shown in **Fig. 2**. The study suggests that the solubility of drug is more in all the non-volatile solvents compared with that in distilled water.

Table 7: Solubility of Lercanidipine HCl in different non-volatile solvents

S.No.	Solvent	Solubility (mg/mL)
1.	Water	0.0889±0.013
2.	Propylene Glycol	5.04±0.12
3.	PEG- 200	7.56±0.36
4.	PEG-400	8.46±0.66
5.	PEG-600	22.56±0.43
6.	Tween 80	13.73±0.33

Data expressed as mean ± s.d. (n=3)

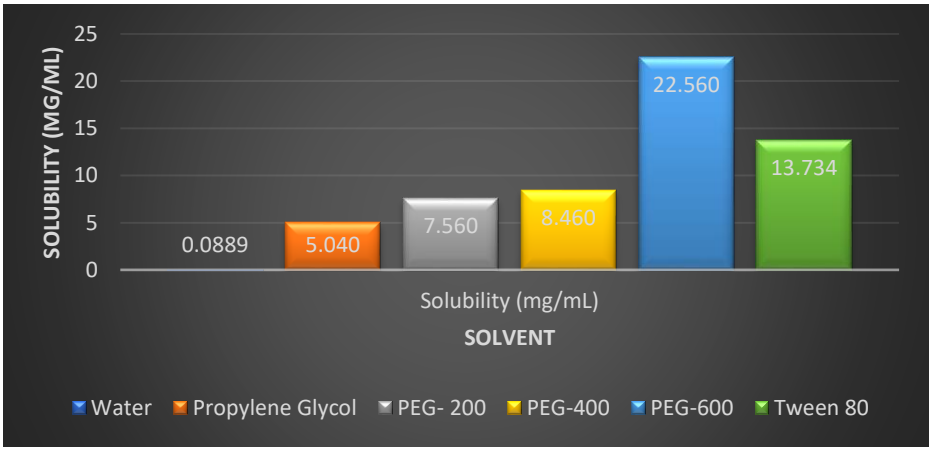

Fig. 2: Solubility of Lercanidipine HCl in different non-volatile solvents

Out of all the non-volatile solvents evaluated, propylene glycol showed least solubility of 5.04 mg/mL whereas maximum solubility of 22.56 mg/mL was observed with PEG 600. Hence PEG 600 and Tween 80 were selected as suitable non-volatile solvents to disperse and dissolve lercanidipine HCl for liquisolid compact formulation in the current investigation.

Preparation of liquisolid compacts of lercanidipine HCl

In the same present investigation twenty-two formulations of liquisolid compacts of lercanidipine HCl were prepared as per the formulae**.** All the liquisolid compacts prepared were found to be fine and free flowing powers.

Micromeritic properties of formulation

Flow properties of the prepared lercanidipine HCl liquisolid compacts were estimated and the results are shown in **Table 8**. Angle of repose values were found to be in the range of 24.77±1.94 to 34.13±1.54 °, the percent Carr's Index for all formulations lies within the

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range of 11.44±0.02 to 15.7±0.03 %. Hausner's ratio was found to be in a range of 1.13±0.02 to 1.19±0.03 indicating acceptable flow properties.

Table 8: Micromeritic properties of liquisolid compacts of lercanidipine HCl

Formulation Code	Bulk density (gm/cc)*	Tapped density (gm/cc)*	Carr's index (%)	Hausner's ratio	Angle of repose*
LLS1	0.484±0.02	0.565±0.08	14.34	1.17	29.81±0.86
LLS2	0.491±0.02	0.568±0.04	13.56	1.16	29.02±0.94
LLS3	0.495±0.01	0.569±0.06	13.01	1.15	26.57±1.18
LLS4	0.445±0.03	0.514±0.08	13.42	1.16	28.21±1.46
LLS5	0.456±0.02	0.526±0.03	13.31	1.15	27.54±0.75
LLS6	0.456±0.02	0.527±0.09	13.47	1.16	28.88±1.05
LLS7	0.488±0.03	0.561±0.05	13.01	1.15	26.73±0.69
LLS8	0.504±0.03	0.583±0.05	15.58	1.18	32.25±1.33
LLS9	0.511±0.02	0.597±0.08	14.41	1.17	30.12±1.41
LLS10	0.447±0.03	0.515±0.07	13.21	1.15	27.36±1.01
LLS11	0.459±0.02	0.529±0.04	13.23	1.15	27.45±0.91
LLS12	0.477±0.02	0.551±0.02	13.43	1.16	28.33±0.65
LLS13	0.489±0.03	0.562±0.02	12.99	1.15	25.97±0.86
LLS14	0.521±0.02	0.612±0.08	15.71	1.19	34.13±1.54
LLS15	0.538±0.02	0.621±0.05	13.37	1.15	28.04±1.62
LLS16	0.449±0.03	0.521±0.07	13.82	1.16	29.74±1.92
LLS17	0.478±0.02	0.553±0.11	13.56	1.16	29.12±0.99
LLS18	0.479±0.04	0.551±0.06	13.07	1.15	27.32±1.07
LLS19	0.542±0.02	0.623±0.04	11.44	1.13	24.77±1.94
LLS20	0.482±0.01	0.563±0.08	14.39	1.17	29.94±1.65
LLS21	0.454±0.02	0.524±0.04	11.67	1.13	25.64±1.71
LLS22	0.551±0.03	0.636±0.02	13.36	1.15	27.67±1.95

***Data expressed as mean ± s.d. (n=3)**

Percent practical yield, drug content, solubility and drug release of liquisolid compacts of lercanidipine HCl

Percentage of practical yield, drug content, solubility and drug released at 30 min for all liquisolid compacts of lercanidipine HCl were estimated and the results are shown in **Table 9** and **Fig. 3**

Table 9: Evaluation Test Results of Lercanidipine HCl Liquisolid Compacts

Formulation	% Practical yield	% Drug content	Solubility (mg /ml)	% Drug released at 30 min
LLS1	98.99±0.13	100.57±0.02	3.38±0.07	44.28±0.12
LLS2	98.23±0.01	97.64±0.12	6.05±0.04	73.33±0.02
LLS3	99.27±0.03	100.33±0.01	5.16±0.02	69.66±0.02
LLS4	99.37±0.01	97.47±0.01	7.82±0.08	95.17±0.13
LLS5	99.26±0.01	100.77±0.02	10.49±0.07	99.66±0.04
LLS6	98.75±0.01	99.96±0.11	9.61±0.09	98.02±0.02

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LLS7	99.96±0.01	99.5±0.12	3.02±0.08	33.22±0.12
LLS8	97.68±0.12	100.52±0.12	5.69±0.05	77.38±0.14
LLS9	99.57±0.12	98.09±0.02	4.81±0.04	63.49±0.12
LLS10	99.26±0.14	97.68±0.16	7.47±0.11	90.69±0.11
LLS11	98.99±0.01	99.57±0.14	10.13±0.08	99.27±0.02
LLS12	99.12±0.02	98.81±0.02	9.25±0.02	95.46±0.02
LLS13	97.71±0.05	98.43±0.14	3.11±0.05	34.21±0.17
LLS14	99.67±0.01	100.37±0.11	5.78±0.08	79.19±0.02
LLS15	98.26±0.12	98.52±0.13	4.89±0.04	65.04±0.01
LLS16	99.21±0.12	99.37±0.01	7.56±0.06	91.93±0.11
LLS17	99.26±0.12	99.26±0.12	10.22±0.08	99.13±0.03
LLS18	98.88±0.02	98.75±0.12	9.33±0.05	96.29±0.03
LLS19	97.21±0.14	98.33±0.12	6.05±0.03	73.39±0.12
LLS20	98.55±0.14	100.12±0.14	9.63±0.04	98.23±0.02
LLS21	98.78±0.11	98.56±0.01	7.47±0.06	90.76±0.14
LLS22	99.26±0.11	98.47±0.02	4.89±0.02	65.53±0.01

Data expressed as mean ± s.d. (n=3)

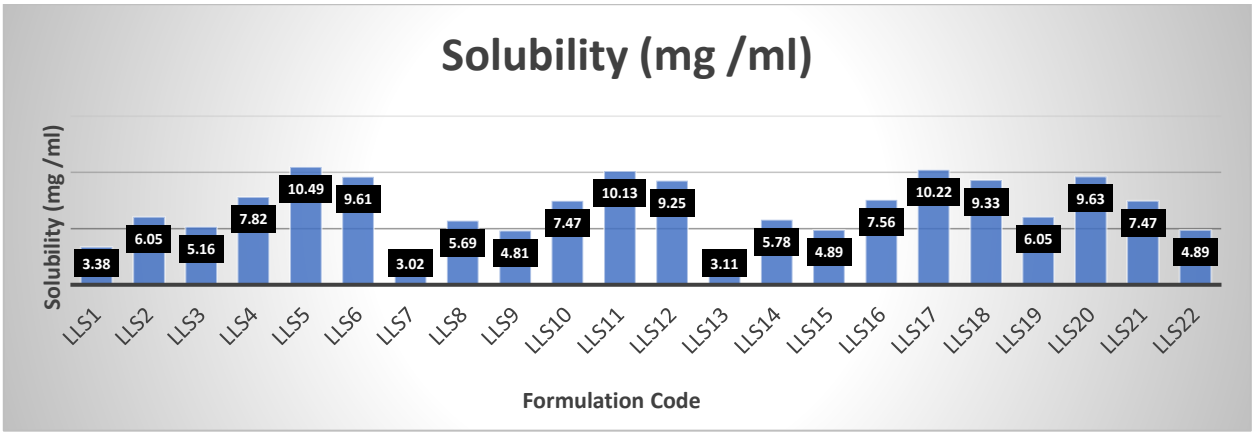

Fig. 3: Solubility of Lercanidipine HCl Liquisolid Compacts

The results of % practical yield for all formulations of liquisolid compacts were found to be in the range of 97.21±0.14 to 99.96±0.01 %. The % drug content of the prepared formulations was found to be in the range of 97.47±0.01 to 100.77±0.02 %. Solubility for all formulations was found to be in the range of 3.02±0.08 to 10.49±0.07 mg/ml. Percent drug released at 30 min for the formulations was found to be in the range of 33.22±0.02 to 99.66±0.01 %.

***In vitro* dissolution studies**

In vitro dissolution studies were performed in triplicate for the prepared formulations and the % drug release data was calculated. The dissolution profiles are shown in **Fig. 4** to **7.**

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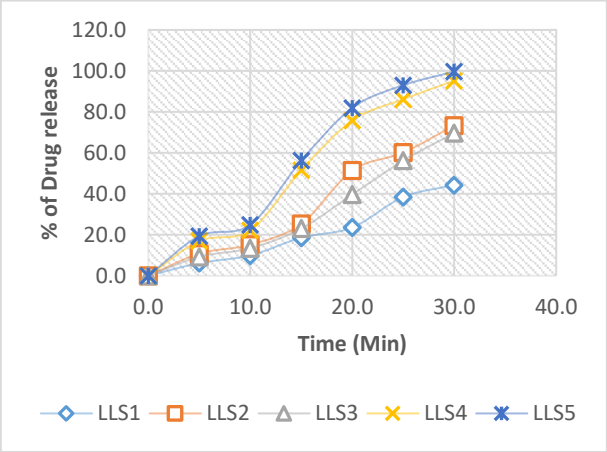

Fig. 4: Dissolution profile of liquisolid compacts of lercanidipine HCl (LLS1 to LLS5)

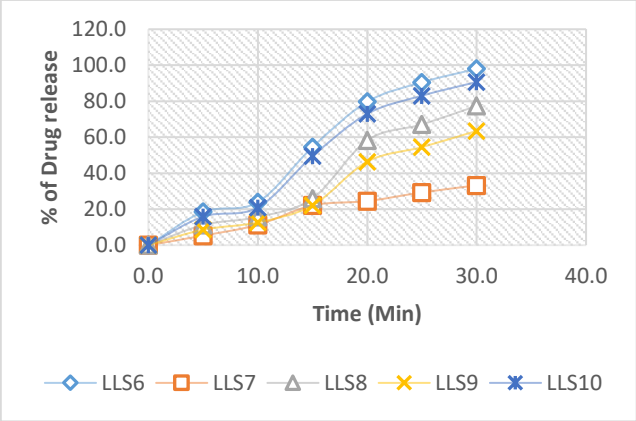

Fig. 5: Dissolution profile of liquisolid compacts of lercanidipine HCl (LLS6 to LLS10)

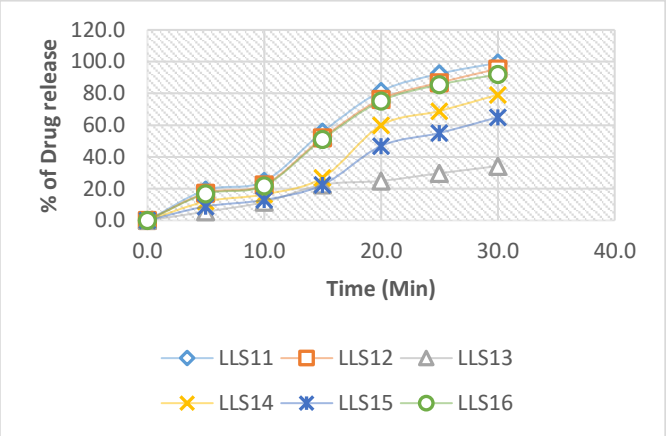

Fig. 6: Dissolution profile of liquisolid compacts of lercanidipine HCl (LLS11 to LLS16)

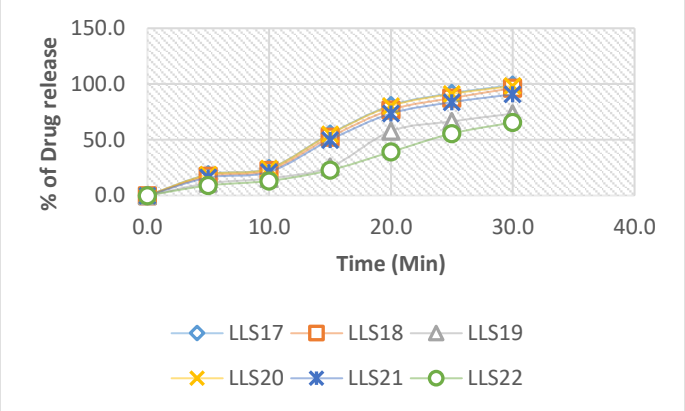

Fig. 7: Dissolution profile of liquisolid compacts of lercanidipine HCl (LLS17 to LLS22)

Statistical optimization of liquisolid compacts of lercanidipine HCl

The responses namely Carr's index, solubility and T30 (% drug released at 30 min) of prepared liquisolid compacts of lercanidipine HCl were fitted to linear, interaction, quadratic and cubic models using the Design Expert 12 software. Of the four models, 2FI (two-factor interaction) model was suggested for all the responses. Model parameters obtained from ANOVA, and fit statistics for the responses are discussed in section 6.7.1 to 6.7.3. These parameters were used to construct models that describe the effect of independent variables on responses.

Data analysis of Response-1: Carr's index

Fit summary, ANOVA and Fit statistics for response-1, i.e. Carr's index are shown in **Table 10** and 11.

Table 10: ANOVA for factorial model of response-1, Carr's index

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Block	20.33	3	6.78			
Model	125.20	13	9.63	4.74	0.0482	significant
A-Non-volatile solvent	15.89	1	15.89	7.82	0.0381	
B-Carrier	25.53	2	12.77	6.28	0.0432	
C-Coating material	20.24	2	10.12	4.98	0.0645	
AB	20.21	2	10.11	4.97	0.0647	

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AC	15.46	2	7.73	3.80	0.0990	
BC	53.66	4	13.42	6.60	0.0314	
Residual	10.16	5	2.03			
Corrected Total	155.68	21				

The Model F-value of 4.74 implies the model is significant. There is only a 4.82% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, BC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

A negative Predicted R^2 implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The obtained ratio of 10.391 indicates an adequate signal. Hence, this model can be used to navigate the design space. The 2D plots and 3D response surface plots for the response-1 (Carr's index) of all formulation factors are shown in **Fig. 8** and **9**

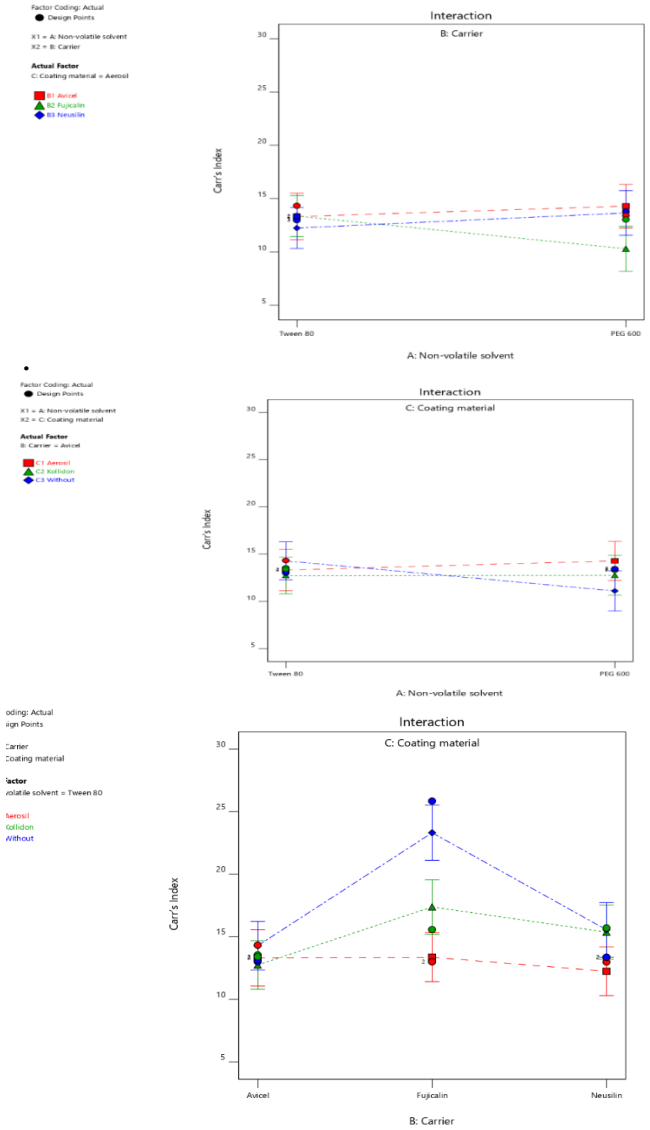

Fig. 8: 2D plots for the effect of various independent variables on Carr's index (Factorial model), liquisolid compacts of lercanidipine HCl:

A *vs* B; A *vs* C; B *vs* C

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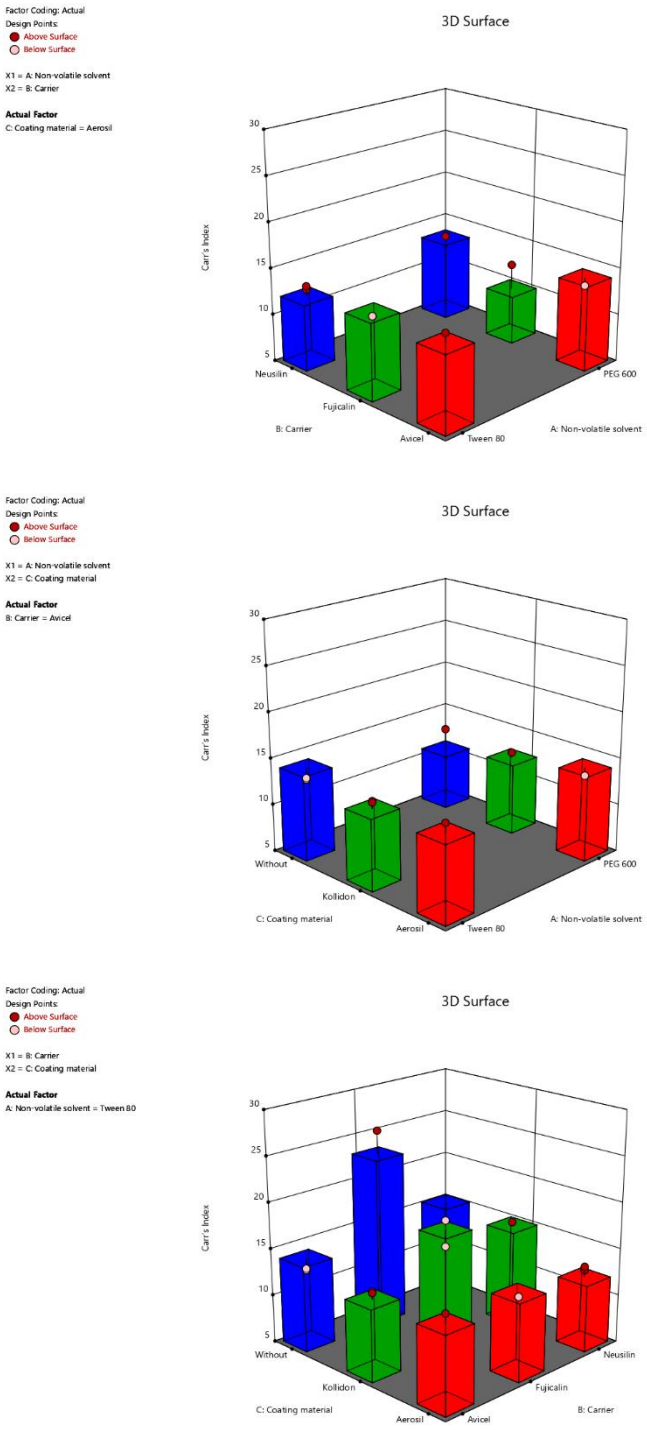

Fig. 9: Response surface plots for the effect of various independent variables on Carr's index (Factorial model), liquisolid compacts of lercanidipine HCl:
A *vs* B; A *vs* C; B *vs* C

Optimization

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The optimized formulation was obtained by applying constraints on dependent variable responses and independent variables. Optimized formulation was selected based on the criteria to attain the minimum Carr's index, maximum solubility and 100% T30 and these constrains are common for all the formulations. Various feasibility and grid searches were executed to establish the optimum formulation. The recommended concentrations of the independent variables were calculated by the Design Expert 12 software which indicated the highest desirability close to 1.0.

The application of response surface methodology (RSM) yielded the following regression equations which give an empirical relationship between the logarithmic values of Carr's index, solubility and T30. Test variables in coded units are A: Non-volatile solvent, B: Carrier, and C: Coating material.

The optimized solution out of 18 results, desirability plot and overlay plot are shown in **Fig. 10** to **12** respectively, with a desirability of 0.993. The values of selected variables obtained from the Design Expert 12 software were PEG 600, Avicel and Kollidon which will give the responses as 12.769 Carr's index, 10.5788 mg/ml of solubility and 98.292% of T30. The working formula for statistically optimized formulation of liquisolid compact of lercanidipine HCl (LLS_{opt}) is presented in **Table 12**. Comparative studies of predicted and observed experimental results as well as coefficient values are shown in **Table 13**.

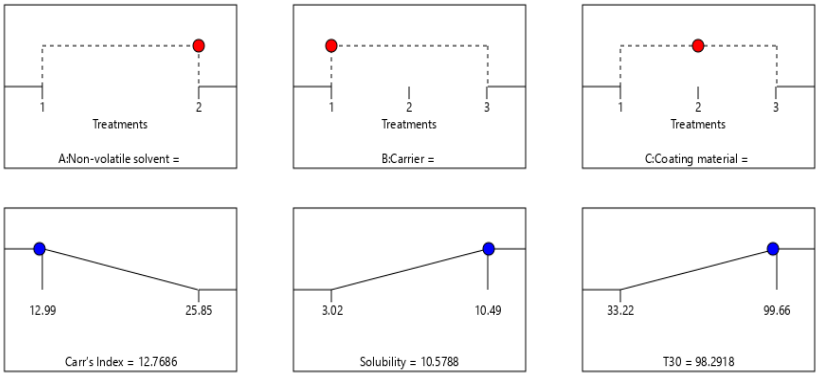

Fig. 10: Optimization results for liquisolid compacts of lercanidipine HCl

Table 12: Formula of statistically optimized formulation, LLS_{opt}

S .No.	Ingredient	Quantity (gm)
1	PEG 600	0.4
2	Avicel	3.0
3	Kollidon	0.15

Table 13: Comparison of predicted and observed responses of statistically optimized formulation, LLS_{opt}

Solution 1 of 18 Response	Predicted Mean	Predicted Median	Observed	Std. Dev.	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
Carr's Index	12.7686	12.7686	12.19	1.4254	1.2570	9.5375	15.9997	2.5648	22.9723
Solubility	10.5788	10.5788	10.28	0.4518	0.3984	9.5547	11.6029	7.3448	13.8129
T30	98.2918	98.2918	98.61	13.3509	11.7731	68.0282	128.555	2.7198	193.864

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Summary

In the current investigation, BCS class II drug, namely lercanidipine HCl was selected to improve their solubility and thereby bioavailability. Lercanidipine HCl is the BCS class-II antihypertensive drug with only 10% bioavailability due to its first pass metabolism. It belongs to dihydropyridine type of calicium channel blocker. It reduces the increased blood pressure by causing vasodilatation. For improving the solubility and dissolution rate of poorly soluble drugs, there are several methods among which liquisolid compact techniques was highly followed and that method was proposed to study their applicability in the current research. For the design and development of formulations, Quality by Design (QbD) approach has been followed with the use of Design of Experiments (DoE).

Preformulation studies were performed to identify the drugs and study their properties in compliance with the literature and compendial specifications. FT-IR spectra and DSC thermogram were analysed to check the characteristic peaks and thermal effects respectively to confirm the drugs. For the selection of excipients, phase solubility studies and non-volatile solvent solubility studies were conducted. Based on the results, Tween 80 and PEG 600 were used as non-volatile solvents; Avicel, Fujicalin and Neusilin were used as carriers; Aerosil and Kollidon were used as coating materials. Based on the trial runs, number of factors and their levels were identified for liquisolid compacts. D-optimal design was selected for formulation of liquisolid compacts of the drug. D-optimal design suggested 22 runs. All the formulations were prepared and evaluated in triplicate. Carr's index, solubility and T30 were selected as responses for liquisolid compacts.

The calibration curve of lercanidipine HCl in 0.1 N HCl was obtained in the range of 4 to 20 µg/ml following Beer Lambert's law at the wave length of 240 nm following UV-Visible spectrophotometer. A good linear relation was observed between absorbance and concentration of lercanidipine HCl. The calibration curve obtained has shown the R^2 value of 0.9989, slope of 0.0529 and intercept of -0.1039. The regression equation for the calibration curve is y = 0.0529x – 0.1039. Micromeritic properties, assay, solubility, *in vitro* dissolution studies, and characterization studies were performed. Obtained responses were given as input to the Design Expert version 12 software, numerical and graphical optimization techniques were followed to analyse the results. 2D contour plots and 3D response surface plots were used to study the interaction studies and ANOVA studies were analysed for statistical optimization. With a desirability value near to 1, the predicted formulae were obtained and the experimental trials were performed in triplicate which has shown relative error within the limits.

Optimized formulations were characterized for drug-excipient compatibility using FT-IR and DSC to understand that there were no chemical interactions. The studies revealed that there is a change of crystalline form to amorphous indicating that as the reason for improved solubility and dissolution of drug with the formulation of liquisolid compacts. Selected optimized formulations were used for stability studies following ICH guidelines at 25±2°C/60±5% RH for long term conditions and 40±2°C/75±5% RH under accelerated conditions for at least 6 months. No significant difference was observed in the evaluated parameters of samples stored at long term and accelerated conditions were overlapping with that of initial sample.

Conclusion

liquisolid compacts of lercanidipine HCl was developed and statistically optimized following DoE along with stability and pharmacokinetic studies. In addition to improving bioavailability, it would also facilitate quick onset of action hence improving patient compliance. This can serve as a novel approach for the treatment of cardiovascular diseases like hypertension. Moreover, the scale-up of this formulation would be easy and can be extrapolated to commercialization. Hence, from the current investigation, it can be concluded that the development of liquisolid compacts of lercanidipine HCl will increase the solubility and dissolution rate there by improving the bioavailability of drug. Applying the QbD approach with DoE has made the investigation more scientific and the optimization process was done with statistical validation.

References

1. Guido Grassi, Nicolàs R. Robles, Gino Seravalle, and Francesco Fici. Lercanidipine in the Management of Hypertension: An Update, Journal of Pharmacology and Pharmacotherapeutics, 2017;8(4):155-165.
2. Mishra V, Thakur S, Patil A, Shukla A. Quality by design (QbD) approaches in current

pharmaceutical set-up. Expert opinion on drug delivery. 2018;15(8):737-758.

3. Nadpara NP, Thumar RV, Kalola VN, Patel PB. Quality by design (QBD): A complete review. Int J Pharm Sci Rev Res. 2012;17(2):20-28.
4. Krtalić I, Radošević S, Hafner A, Grassi M, Nenadić M, Cetina-Čižmek B, Filipović-Grčić J, Pepić I, Lovrić J. D-optimal design in the development of rheologically improved in situ forming ophthalmic gel. Journal of Pharmaceutical Sciences. 2018;107(6):1562-71.
5. Shaikh F, Patel M, Shelke S, Patel V, Jani D, Shinde G, Pathan I. Formulation, Characterization, Optimization, and Pharmacokinetic Evaluation of Cilnidipine-Loaded Liquisolid Compacts with Improved Dissolution and Bioavailability. Journal of Pharmaceutical Innovation. 2023 Jun;18(2):404-25.
6. Saini S, Garg R. Design expert assisted mathematical optimization of solubility and study of fast disintegrating tablets of Lercanidipine Hydrochloride. Journal of Drug Delivery and Therapeutics. 2019 Feb 15;9(1-s):172-80.
7. Reddy N, Dugasani S, Nayakanti D. Fabrication And Assessment Of Lercanidipine Hydrochloride Solid Dispersions For Solubility Preferment Using Polymer Combination. Asian J Pharm Clin Res. 2021;14(7):77-81.
8. Jaydip B, Dhaval M, Soniwala MM, Chavda J. Formulation and optimization of liquisolid compact for enhancing dissolution properties of efavirenz by using DoE approach. Saudi Pharm J. 2020 Jun;28(6):737-745.
9. Prajapati B, Rao S, Barot T. Development of Solid Self Microemulsifying Drug Delivery System (S-SMEDDS) of Aripiprazole by using D-Optimal Mixture Design. High Technology Letters. 2020;26:721-31.