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PREPARATION, EVALUATION AND OPTIMIZATION OF LERCANIDIPINE HYDROCHLORIDE FILMS

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ABSTRACT

Background: Lercanidipine hydrochloride (LER) is a BCS class II antihypertensive drug which results in limited oral bioavailability of 10%.**Aim:** The purpose of this study is to improve the dissolution and thus the bioavailability of LER by preparing films of LER. The objectives of the project are: To increase the solubility of Lercanidipine. Development of Lercanidipine oral fast dissolving films by use of various grades and concentrations of HPMC. Evaluation of Lercanidipine oral films by dissolution, disintegration, folding endurance and thickness studies. **Method:** The films were prepared by the box-behnken method by using solvent casting method. Films obtained showed improved release compared to pure LER and physical mixture. **Results:** It can be confirmed from the obtained results that films can be a method of choice for increasing the solubility, dissolution and in turn the bioavailability of Lercanidipine hydrochloride. **Conclusion:** Optimized films have showed increased dissolution of lercanidipine Hcl up to 99% w/w after 10 min and its solubility had increased upto 180 times. The obtained results had shown that there was increased dissolution and bioavailability of LER films and could give quick onset of action upon administration of lercanidipine hydrochloride oral fast dissolve films.

INTRODUCTION

Lercanidipine is the BCS class – II antihypertensive drug. It belongs to dihydropyridine type of calcium channel blocker. It reduces the increased blood pressure by causing vasodilatation. It acts by relaxing vascular smooth muscle to lower peripheral resistance. LER has only 10% of bioavailability due to first pass metabolism. So, it requires enhancement of dissolution rate and bioavailability to attain its maximum therapeutic efficiency.[1]

HYPERTENSION: [2] High blood pressure also called hypertension. It is a common disease that occurs when the pressurein the arteries is higher, if the pressure remains Consistently high it may cause many complications in the body. Blood pressure of 130/80 mm Hg or higher then you will mostly like to be diagnosed with high blood pressure. It can lead to severe health disease, stroke and sometimes death.

Types of Hypertension:

1) Primary hypertension:

This type of hypertension doesn't have any identifiable cause of high blood pressure. It occurs mostly in adults.This may tends to develop gradually into secondary hypertension over many years.**2) Secondary hypertension:** Secondary hypertension is caused by underlying condition and may occur during pregnancy time also.

SOLUBILITY:[3,4, 5, 6, 7]

Solubility is an intrinsic property of any dosage form. Solubility of any drug product can be defined as both quantitatively and qualitatively. Quantitatively it is defined as that milligram of solute particles required to make a saturated solution. Qualitatively it is defined as where two phases are mixed together to form a homogeneous solution.

Reasons for active compound possessing low aqueous solubility:

- High molecular weight and lipophilicity of a compound result in decrease in aqueous solubility of a compound.
- Compounds with log P value ≥2.
- Molecular weight of compound is > 500 Daltons.
- When the active compound containing five or more carbon atoms.

IP, BP, USP has defined the solubility as in given table

Classification of drugs based on aqueous solubility:[6]

Classification system of active substances based on their aqueous solubility and membrane permeability is called as Biopharmaceutical classification system. Aqueous solubility and permeability plays an important role in oral bioavailability.

ORAL FAST DISSOLVING FILMS:[8-13]

Rapid or fast dissolving oral thin film is becoming an increasingly popular drug delivery system because the film dissolves within a few seconds on contact with saliva. As most of the polymers used in oral films are amorphous, they aid rapid dissolution without the need of water. As a result of these advantages, OFDF are mostly suitable for paediatric and geriatric patients.[9]

Need for Oral Fast Dissolving Films: Oral fast dissolving films [OFDF] is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self-administration, without water or chewing. Oral films are developed as the oral drug delivery systems still need some advancement to be made because of their some drawbacks related to particular class of patients which includes geriatric, paediatrics and dysphasic patients associated with many medical conditions as they have difficulty in swallowing. Even with fast dissolving tablets there is a fear of choking but in oral dissolving film there is no risk of choking. The fast dissolving action of the film is primarily due to its large surface area which wets quickly when exposed to the moist oral environment. Films are also useful whether local action desired such as local anaesthetic for toothaches, oral ulcers, cold sores or teething.

Formulation Ingredients of OFDF:

Several classes of drugs can be formulated as mouth dissolving films including antihistaminic (Salbutamol sulphate), antiulcer (Omeprazole), NSAID'S (Valdecoxib, Meloxicam, etc.), expectorants and antitussives.

METHODS

PREFORMULATION STUDIES:

Pre-formulation studies are an investigation of physical and chemical properties of the drug substances alone and combined with excipient like colour, form, melting point, and solubility studies, micrometric properties, compatibility studies, analytical studies etc.

MELTINGPOINT: Melting point of lercanidipine was determined by using melting point apparatus.

SOLUBILITY: The solubility of Lercanidipine was studied by using different carriers such as soluplus, polaxamer188, PEG 6000, phosphate buffers pH 1.2, 4.5, 6.8, water, urea, etc. Required quantity of drug was taken in a 20ml volumetric flask and carriers were added to the flask. Flask with drug and carrier mixture was placed in a rotary shaker for 24hrs, by maintaining desired conditions for uniform distribution of drug in the solvent and to enhance the solubility of drug. The contents of flasks were centrifuged at 50rpm and were filtered. The obtained filtrate was estimated under U.V. visible Spectrophotometer at 242nm.

MICROMERITIC PROPERTIES:[20-25]

Bulk Density: The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder

bed. The bulk density is expressed in grams per millilitre (g/ml).

Procedure: Accurately weighed 1g of lubricated granules was through a 20# sieve to break up agglomerates that may have formed during storage; this process must be done gently to avoid changing the nature of the material. Into a 50 ml dry graduated cylinder slowly introduce the powder to be tested and carefully level the powder without compacting and read unsettled apparent volume (V_o). Bulk density is calculated by below formula:

Bulk density = Weight of powder/Bulk volume

Tapped density: The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample.

Procedure: Accurately weighed 1g of lubricated granules was through a 20# sieve to break up agglomerates that may have formed during storage. And then granules were transferred through a 50 ml dry graduated cylinder equipped with a cap. The measuring vessel with the cap is lifted 50-60 times per minute by the use of a suitable tapped density tester. The taps were carriedout for 200 times and measure the tapped volume (V_1). Tapping procedure was repeated for additional 400 times and measure the tapped volume (V_2). If the difference between the two masses obtained after 200 and 400 taps exceeds 2%, carry out a test using 200 additional taps until the difference between succeeding measurements is less than 2%. Calculate the tapped density (g/ml) using the formula:

Tapped density = Weight of powder/tapped volume

Angle of repose: Angle of repose is the maximum possible angle between the surface of pile of powder and the horizontal plane.

Procedure: Accurately weighed powder was passed through a funnel which results in formation of pile of powder. The height of the pile (h) is recorded and radius of the pile (r) is then measured. The Angle of repose is calculated by the following formula:

$$\tan \Theta = {}^{h}/_{r}$$

Carr's index: The Carr index (Carr's Compressibility Index) is an indication of the compressibility of a powder. The Carr index is calculated by the formula

$$\textit{Carr's index} = \frac{\textit{tapped density} - \textit{bulk density}}{\textit{bulk density}} \times 100$$

Hausner's ratio: Hausner's ratio is used to predict the propensity of a given powder sample to be compressed. It can be calculated by the given formula:

Hausner's Ratio = V_o/ V_f

Where,

V_o = original bulk volume of powder

V_f = final tapped volume of powder

ANALYTYCAL STUDIES:

Calibration curve of Lercanidipine in 0.1N HCL:

Preparation of 0.1N HCL: 8.5ml of HCL is dissolved in 1000ml of water in 1000ml volumetric flask.

Preparation of stock solution: Stock solution was prepared by dissolving 10mg of Lercanidipine in 10ml of ethanol (mg/ml). 1ml of the above solution was taken in 10ml volumetric flask.To this 6ml of 0.1N HCL was added, shaken for 20 min. Volume was made up to 10ml using 0.1N HCL solution (100µg/ml).

Preparation of standard solution: Different aliquots were taken from stock solution in to 10ml volumetric flask. To this 6ml of 0.1N HCL was added, shaken for 20mins and sonicated for 5mins. Volume was made up to 10ml using 0.1N HCL solution to prepare the series of concentration 5,10,15,20,25µg/ml. Absorbance of these solution were measured at λ max 242 nm using UV-Visible spectrophotometer and standard plot was plotted between concentration on X-axis and absorbance on Y-axis which gives straight line.

MANUFACTURING METHODS:[14-16]

Preparation of Oral Fast Dissolving Films of Lercanidipine: The oral fast dissolving films were designed through Box behnken design and were prepared by **solvent-casting** method using HPMC E3(X_1), E5(X_2)and E15(X_3) as film base with different concentrations. PEG400 was used as plasticizer, and citric acid was used as saliva stimulating agent. Polymers, citric acid were added to water and stirred for 2 minutes on a magnetic stirrer. Drug solution was added to the above solution under continuous stirring for 2minutes and sonicated for 5 minutes to remove air bubbles. This solution was casted on a Petri dish and dried. The films were carefully removed from Petri dish, checked for any imperfections and cut

into 2×2 cm^2. The samples were stored in desiccators for further analysis. In the current investigation 17 formulations were prepared and their composition was listed in below table. The prepared OFDF were evaluated for % practical yield, thickness, folding endurance, dissolution and disintegration.

EVALUATING METHODS: [22, 23]

Evaluation of Lercanidipine OFDF: Lercanidipine oral fast dissolving films obtained are tested for percentage practical yield, thickness, folding endurance, disintegration and dissolution.

% Practical Yield: Percentage practical yield was calculated to know about percentage yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation. **% Practical Yield = (Practical mass / Theoretical mass) × 100**

THICKNESS: The thickness of the different films was measured using a calibrated thickness gauge with an accuracy of 0.001 mm. The film was placed in between anvil and pressor foot of thickness gauge and the reading on the dial was noted down. The estimations were carried out in triplicate and the average is calculated. Uniform thickness of film is essential as it is directly related to accuracy of dose distribution in the film.

FOLDING ENDURANCE: Folding endurance is a procedure to estimate the mechanical properties of a film and it also gives an indication of brittleness of film. It was determined by repeated folding of the film at 180º angle of the plane at the same place till the film breaks. The number of times the film was folded without breaking was computed as the folding endurance value. The estimations were carried out triplicate manually. A direct relation exists between mechanical strength and folding endurance of films. As mechanical strength depends on concentration of plasticizer it is clear that, the folding endurance value is indirectly affected by concentration of plasticizer.

DISSOLUTION: The in-vitro dissolution studies were conducted using pH 6.8 buffer as dissolution medium and about 100ml of pH 6.8 buffer was taken in an 125 ml beaker. A film (2×2 sq.cm) was placed in a beaker. Medium was stirred at 50 rpm by maintaining 37 º c temperatures using magnetic stirrer bar. 5ml samples were withdrawn at 2, 4, 6, 8, 10 min time intervals and every time replaced with 5ml fresh dissolution medium. The samples were analysed by measuring U.V. absorbance at 242nm.

DISINTEGRATION: Disintegration time of film is the time required by oral film to start breaking when brought in contact with water or saliva. The disintegration time depends upon the composition of the films. Generally, it ranges from 5-30 seconds. There are no official guidelines to determine the disintegration time of oral films. One of the methods is dipping the film in 25 ml water or saliva in a beaker. The beaker should be shaken gently and the disintegration time was noted.

***IN VITRO* WETTING TIME:** A paper was placed in a petriplate and 6ml of 0.1%w/v amaranth dye solution was added to it. The film strip was placed on the surface of tissue paper. Then the time required for the dye to appear on the surface of the film was noted as the wetting time.

RESULTSSOLUBILITY STUDIES:

Solubility of LER was studied in different polymers like Soluplus, Kolliphor;PEG 6000, PVP K30, water, phosphate buffers pH 1.2, 4.5, 6.8. From this study, among all the solvents and carriers used in preliminary solubility studies the drug shown high solubility in soluplus and low solubility was seen in water The graphical representation of solubility studies of Lercanidipine Hydrochloride physical mixtures was shown in **Figure**

IN-VITRO DISSOLUTION STUDIES: The drug release data obtained for formulations F1 to F18 are tabulated in **Table.** It shows the cumulative percentage of drug released as a function of time for all formulations. In vitro studies reveal that there is marked increase in the dissolution rate of LER Hydrochloride from all the films when compared to pure LER Hydrochloride itself.

Optimization of Oral Fast Dissolving Films: The selected independent variables were HPMC E_3, HPMC $E_5$and HPMC E_{15} which were selected at three different levels low, medium, high. Other parameters like concentration of drug, citric acid, PEG 400 were kept constant to minimize the fluctuations. The 17 runs were evaluated for

responses: Dissolution (Y_1), Disintegration (Y_2), Folding endurance (Y_3).The formula generated by using Design-Expert software version 12 is with minimum disintegration, maximum dissolution and maximum folding enduranc

Table- 1: Solubility description table

Description	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Insoluble	More than 10000

Table-2: Biopharmaceutical classification system

Classification	Property	Examples
BCS class – I	Highly soluble, highly permeable	Benzapril, sumatriptan
BCS class – II	Low soluble, highly permeable	Metaprolol, Lercanidipine
BCS class – III	Highly soluble, low permeable	Atropine, Topiramate
BCS class – IV	Low soluble, low permeable	Hydrochlorothiazide

Table-3 Classification and Properties of OFDF

Properties	Flash release wafer	Muco adhesive melt away wafer	Muco adhesive sustained release wafer
Area	2-8	2-7	2-4
Thickness	20-70	50-500	50-250
Structure	single layer film	single/multilayer system	Multilayer system
Excipients	Soluble &hydrophilic polymers	Soluble &hydrophilic polymers	Low/ non-soluble polymers
Drug phase	Solid solution	solid solution or suspended drug particle	solid solution/ suspension
Application	Tongue	Buccal region	Gingival
Dissolution	Maximum 60 sec	Disintegrates within few minutes,forming gel	Max 8-10 hrs
Site of action	Systemic or local	systemic or local	Systemic or local

Table-4: Composition of OFDF

Drug	5% to 30%
Water soluble polymer	45% w/w
Plasticizers	0-20%w/w
Sweetening agent	3 to 6%
Saliva stimulating agent	2 to 6% w/w
Surfactant	q.s.
Fillers, colours, flavours	q.s.

Table-5: Codes of Box- Behnken design

Independent variables	Levels		
	Low	Medium	High
HPMC E15 (X_1)	-1	0	1
HPMC E5(X_2)	-1	0	1
HPMC E3 (X_3)	-1	0	1

Where, -1 = 0 mg, 0 = 20 mg, 1 = 40 mg

Table-6: Compositions of LER OFDF

Formulations	Ingredients (mg)							
	Drug	HPMC E15	HPMC E5	HPMC E3	PEG 400	Citric acid	Methanol	Distilled Water
F1	5	20	20	20	15	6	q.s	q.s
F2	5 mg	0	40	20	15	6	q.s	q.s
F3	5 mg	40	20	0	15	6	q.s	q.s
F4	5 mg	20	20	20	15	6	q.s	q.s
F5	5 mg	20	20	20	15	6	q.s	q.s
F6	5 mg	20	0	0	15	6	q.s	q.s
F7	5 mg	0	20	40	15	6	q.s	q.s
F8	5 mg	20	40	40	15	6	q.s	q.s
F9	5 mg	0	20	0	15	6	q.s	q.s
F10	5 mg	20	20	20	15	6	q.s	q.s
F11	5 mg	40	20	40	15	6	q.s	q.s
F12	5 mg	20	40	0	15	6	q.s	q.s
F13	5 mg	40	40	20	15	6	q.s	q.s
F15	5 mg	20	0	40	15	6	q.s	q.s
F16	5 mg	20	20	20	15	6	q.s	q.s
F17	5 mg	40	0	20	15	6	q.s	q.s

Table-7: PREFORMULATION STUDIES:

Parameter	Results
Colour	Yellow
State	Crystalline
Melting point	186ºc
Solubility	Soluble in methanol, ethanol, acetone. Poorly soluble in water
Micromeretic Properties	
Bulk density	0.98g/ml
Tapped density	0.71g/ml
Angle of repose	37.64º
Carr's index	27.5%
Hausner's ratio	1.38

Table-8: Standard Curve For Ler Hcl In Phosphate Buffer Ph1.2:

S.no	Concentration (µg/ml)	Absorbance			Average
		T1	T2	T3	
1	5	0.131	0.128	0.124	0.128 ± 0.0035
2	10	0.315	0.319	0.321	0.318 ± 0.003
3	15	0.531	0.522	0.516	0.523 ± 0.007
4	20	0.741	0.739	0.740	0.740 ± 0.001
5	25	0.987	0.991	0.981	0.986 ± 0.005

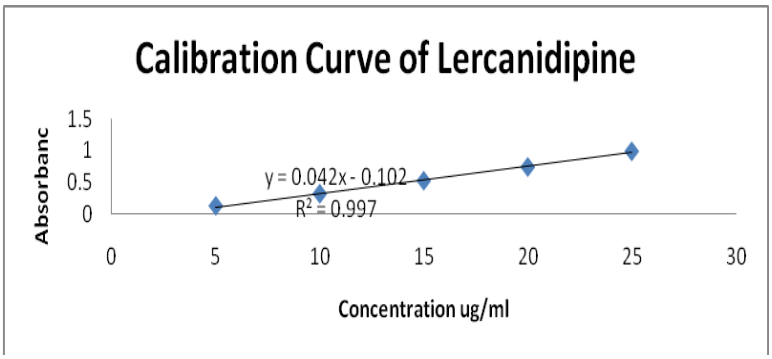


Fig- 1: Standard Curve For Lercanidipine In Phosphate Buffer Ph 1.2

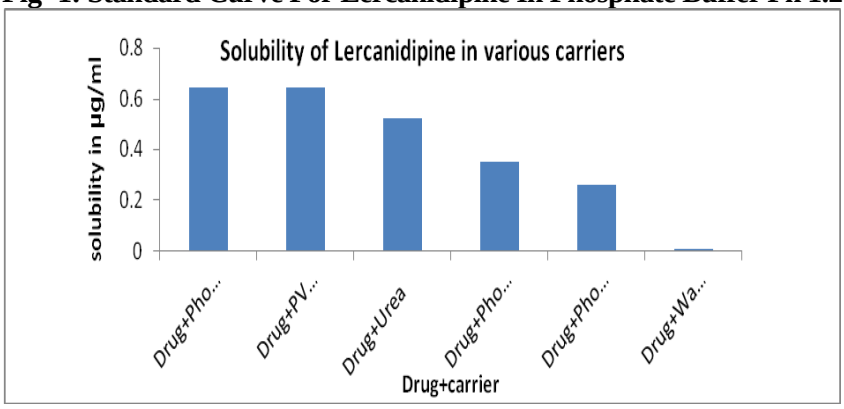


Fig- 2:Solubility studies of Lercanidipine Hydrochloride physical mixture in 1:1 ratio

Table-9: Results of OFDF of LER HCl containing evaluating parameters as %practical yield, thickness, folding endurance, disintegrating time, wetting time:

FORMULATION	EVALUATION PARAMETERS				
	%Practical yield	Thickness µm	Folding endurance	Disintegration time in sec	Wetting time in sec
F1	97.26	162±21.0	269±15	17±1.0	12
F2	97.7	324±21.6	258±5.0	33±1.0	26
F3	91.7	284±1.15	274±3.2	17±1.0	17
F4	97	160±9.0	264±5.2	30±0.6	19
F5	94.84	244±2.6	263±5.0	30±1.0	28
F6	92.06	210±4.5	245±10.0	40±1.5	14
F7	94.41	152±9.0	253±7.3	33±0.2	33
F8	93.41	125±18.0	275±4.0	16±0.7	11
F9	97.06	256±6.6	243±4.5	55±1.5	37
F10	97.29	190±25.2	262±6.0	31±0.4	20
F11	96.54	393±14.9	275±6.1	15±2.6	18
F12	90.05	261±6.0	271±4.0	16±0.5	16
F13	98.8	327±24.7	280±11.7	10±0.2	25
F14	99.34	161±7.0	241±2.0	63±0.1	29
F15	92.81	294±15.0	259±6.5	31±1.3	34
F16	98.72	180±9.6	261±14.7	30±0.8	21
F17	92.84	344±9.5	273±4.0	17±0.1	15

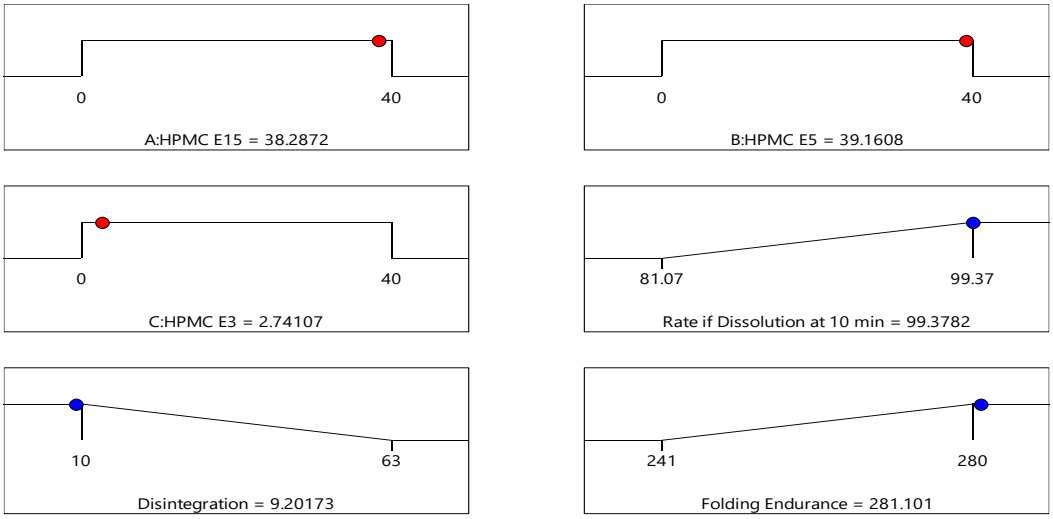
Table-10: *In vitro* dissolution profile of different formulations of Lercanidipine Hydrochloride OFDF (F1-F8)

Time in min	Cummulative % drug dissolved							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	29.48	28.3	24.46	30.9	24.3	29.4	29.4	37.63
4	35.51	33.3	38.54	43.1	42.6	38.5	47.08	50.17
6	43.24	44.2	49.91	47.8	53.4	44.9	49.46	57.92
8	65.53	67.1	68.23	53.8	67.7	49.5	70.93	78.54
10	87.9	97.1	99.37	99.21	85.2	94.5	90.63	95.49

Table-11: In vitro dissolution profile of different formulations of Lercanidipine Hydrochloride OFDF (F9-F17)

Time in min	Cummulative % drug dissolved								
	F9	F10	F11	F12	F13	F14	F15	F16	F17
0	0	0	0	0	0	0	0	0	0
2	43.1	35.33	22.6	29.7	21.29	30.3	47.46	49.3	29.7
4	51.1	44.80	42.1	43.07	29.48	42.4	57.27	57.05	41.9
6	57.4	63.15	53	45.9	42.22	46.8	65.20	61.5	45.4
8	65.4	90.95	76.76	53.5	49.37	53.3	83.02	73.9	52.4
10	98.08	95.06	98.7	92.09	81.07	91.6	92.52	93.3	90.0

The optimised formula was:



Desirability = 1.000
Solution 1 out of 100

Table-12: Optimised formula of LER OFDF

Independent variables		Dependent variables	
Name	Quantity	Name	Predicted result
HPMC E15 (X1)	38.2872	Rate of dissolution at 10 min (Y1)	99.3782
HPMC E5 (X2)	39.1608	Disintegration in sec (Y2)	9.20173
HPMC E3 (X3)	2.74107	Folding endurance (Y3)	281.101

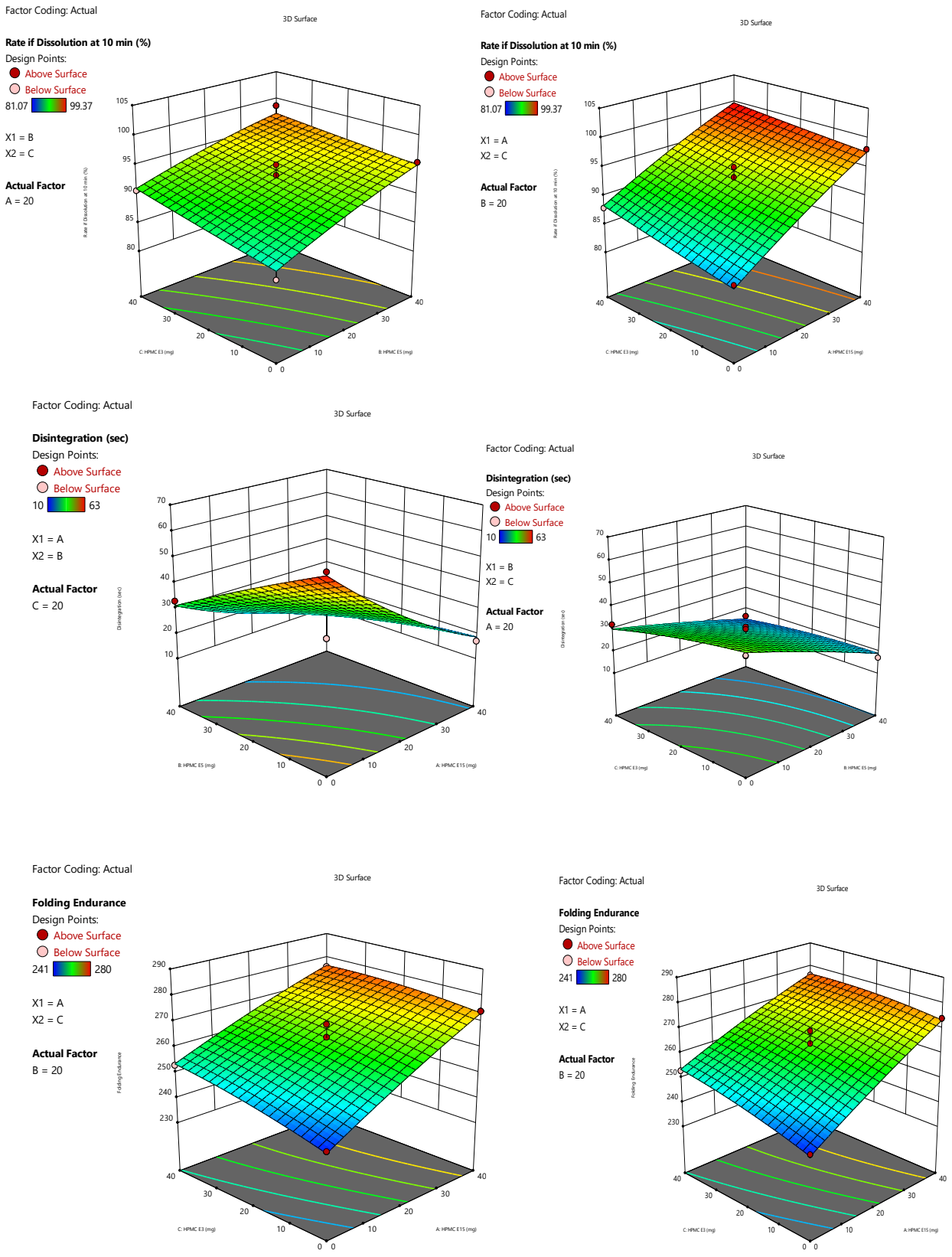


Fig -3 to 8: Contour plots for influence of variables on dissolution, disintegration and folding endurance

EVALUATION OF OPTIMISED FILM:

Table-13: Results

Parameter	Obtained results
Colour	Pale yellow
Appearance	Transparent
% Practical yield	99.29%
Thickness	250µm
Folding endurance	279.86
Dissolution	99.21%
Disintegraton	10 sec
Wetting time	15 sec

DISCUSSION

In the present investigation, Oral fast dissolving films(OFDF) of Lercanidipine Hcl were formulated by using HPMCE15(X_1), HPMC E5(X_2), HPMC E3(X_3) as independent variables.The OFDF were developed by using Box-Behnken method and prepared by solvent casting method. The prepared films were evaluated for % practical yield, Folding endurance, Thickness, Disintegration, Dissolution studies and In-vitro wetting time.Based on the solubility studies conducted to physical mixtures of LER Hcl it was declared that LER Hcl has highest solubility in PH 1.2 phosphate buffer where as it has least solubility in water. The films obtained were pale yellow in colour and transparent in nature. % Practical yield for the films was in the range of 90.2 – 99.34%. Folding endurance of films was in the range of 241±2 to 280±11.7. Thickness for the obtained films was found to be in between 125±18 to 393±14.9. Disintegration time for the OFDF was in the range of 10±0.2 to 63±0.1. Percentage of drug dissolution for the prepared films was found to be in the range of 81.07 to 99.37. In-vitro wetting time was in the range of 11 to 37 seconds. The optimised formulation developed has shown maximum dissolution rate, minimum disintegration time and maximum folding endurance. It shows 90% more solubility and dissolution rates when compared to pure drug.

SUMMARY AND CONCLUSION

The current investigation established an effective and easy method to formulate lercanidipine Hcl films to increase its water solubility and also its dissolution. OFDF were prepared by solvent casting method through Box-Behnken design. OFDF proved to have the best results in terms of solubility and dissolution. Optimized films have showed increased dissolution of lercanidipine Hcl up to 99% after 10 min. The results obtained confirm that films would improve the oral bioavailability of lercanidipine Hcl. The rise in dissolution efficiency could give quick onset of action after oral administration of the lercanidipine Hcl. In addition of 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.

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