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Enhancement of Solubility and Dissolution Rate of Lacidipine Solid Dispersion Technique by Solvent Evaporation Method

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ABSTRACT:

The present study was aimed in developing the solid dispersion studies of combination of the polymers like PEG 6000: PEG 4000 prepared by solvent evaporation technique with ratio of Drug and polymer ratio was 1:1:1. The Lacidipine solid dispersion were evaluated for physicochemical characteristics like drug content and in vitro drug release studies. Form FTIR studies, it concluded that there was no chemical interaction between the drugs and polymers like PEG 6000 and PEG 4000. it can provide promising way to enhance its solubility and dissolution rate. The compatibility of the drug and excipients was confirmed by DSV and XRD analysis which clearly compatibility of the polymer and drug. The optimized formulation F1 was Compared with the marketed formulation the F1 shows the In vitro drug release at 99.87% at 140 min. based on the mathematical models, the concluded that formulation F1, the regression value found to be 0.9906 fitted with Higuchi model follows Fickian diffusion and suggests that drug release occurs through diffusion through dispersed vesicles.

Key Words: Solid dispersion technique, polymers, solubility, dissolution rate, solvent evaporation method, drug release

1. Introduction

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Moreover, certain combinations can be encountered, i.e. in the same sample; some molecules are present in clusters while some are molecularly dispersed. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.[1]

Fairly soluble drugs in gastrointestinal media exhibit complete oral absorption,and thus good bioavailability. About 40% of drugs are not soluble in water in practice and therefore are slowly absorbed, which results in insufficient and uneven bioavailability and GI toxicity. Thus, most exigent phase of drug development practice particularly for oral dosage forms is the enhancement of drug solubility thereby its oral bioavailability. Bioavailability refers to the limit of therapeutically active drug that approaches the systemic circulation and thus, is available at the site ofaction. There are two reasons proposed for poor aqueous solubility of drugs [2]

i. High lipophilicity
ii. Strong intermolecular forces which cause the insolubilization of drugs.

Various approaches have been proposed to enhance solubilisation of poorly water soluble drugs for the improvement of their bioavailability commonly used for drug solubilization includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilisation and hydrotropy.[3]

Lacidipine is a lipophilic dihydropyridine calcium antagonist with an intrinsically slow onset of activity. Due to its long duration of action, lacidipine does not lead to reflex tachycardia. It displays specificity in the vascular smooth muscle, where it acts as an antihypertensive agent to dilate peripheral arterioles and reduce blood pressure. Compared to other dihydropyridine calcium antagonists, Lacidipine exhibits a greater antioxidant activity which may confer potentially beneficial antiatherosclerosis effects. It having Chemical formulae $C_{26}H_{33}NO_6$. it is chemically called as diethyl 2,6-dimethyl-4-[2-[(*E*)-3-[(2-methylpropan-2-yl) oxy]-3-oxoprop-1-enyl]phenyl]-1,4-dihydropyridine-3,5-dicarboxylate.[4]

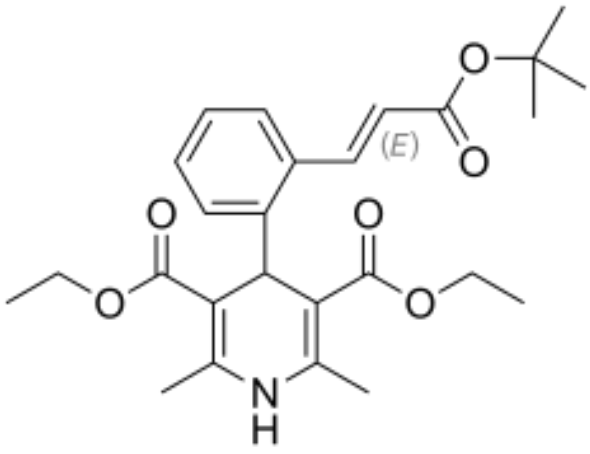

Figure1: Chemical Structure of Lacidipine

Experimental Work:

2. Materials and Methods

Lacidipine pure sample was gifted from the Micro labs Bangalore. all the polymers like PEG – 6000, PEG – 4000, was purchased from Qualikems fine chem. Pvt. Ltd., Vadodara. The chemicals and solvents Methanol, Anhydrous di sodium hydrogen phosphate, SLS, Ortho-Phosphoric acid were purchased from the Loba chem limited. All the instruments were used in the work are calibrated.

Methods:[7-10]

Preformulation studies

Preformulation study is defined as "investigation of physical and chemical properties of the drug substance alone and combined with the excipients". Preformulation studies are the first step in the rational development of dosage form of drugs. It involves the application of biopharmaceutical principles to the physicochemical parameters of the drug with the goal of designing an optimum delivery system that is stable, bioavailable and can be mass produced.

Melting point by capillary tube method

The melting point of Lecidipine was determined by the capillary tube method. A sufficient quantity of Lecidipine powder was filled into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in an electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Lecidipine in the tube passed into liquid phase

Drug-Excipient Compatibility Studies

The drug and excipients selected for the formulation were evaluated for physical and chemical compatibility studies.

Physical compatibility study

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and excipients and placed at room temperature, 40ºC and 75% RH. Any colour change of the physical mixture was observed visually.

S. NO	INGREDIENTS
1	Drug
2	Drug + PEG 6000
3	Drug + PEG 4000
4	Drug + PEG 6000 + PEG 4000

Table2 Composition of drug and excipients for FTIR spectra

Solubility studies of pure Lecidipine

Preformulation solubility analysis was done, which include the selection of suitable solvent, to dissolve the respective drug. The solubility was done by adding the solute in small incremental amounts to the fixed volume of solvents, after each addition, the system was vigorously shaken and examined visually for the undissolved solute particles. When some amount of the solute remains undissolved, the total amount added up to the point served as a good and rapid estimate of solubility.

Construction of Standard Calibration Curve of Lacidipine

Spectrophotometric method for the estimation of Lacidipine by spectrophotometric method

Standard Stock solution: A 1000 µg/ml stock standard solution was prepared by dissolving the 100mg of pure Lacidipine in small amount of methanol and then make up with Phosphate buffer(ph7.0) with 0.5%SLS up to 100 ml.

Secondary stock solution: From the primary stock solution 10ml was accurately pippetted out and transferred into a standard flask and made up to 100ml using Phosphate buffer(ph7.0) with 0.5%SLS, we get 100µg/ml of stock solution. From that sample prepare 10, 20, 30, 40, 50, 60µg/ml solutions.

The standard calibration curve of Lacidipine yields a straight line, which shows that the drug follows Beer's law in the concentration range of 0.5 to 2.5 µg/ml at 252 nm, a standard graph was plotted by keeping the known concentration on X – axis and obtained absorbance on Y – axis.

Preparation of Lacidipine Solid Dispersion technique [11-18]

Formulation	**Drug and Polymer**	**Drug to polymer ratio**	**Methods**
F1	Lacidipine: PEG6000: PEG4000	1:1:1	Solvent evaporation
F2		1:1:2	
F3		1:1:3	
F4		1:1:4	
F5		1:1:5	
F6		1:1:6	
F7		1:1:7	
F8		1:1:8	

Table 3 Preparation of solid dispersion of Lacidipine

Solid Dispersion of Drug: Polymer Ratio 1:1:1(F1) (PEG6000: PEG4000)

500mgof PEG-6000and 0.5 g PEG-4000 was weighed and added to 10ml of methanol and stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beaker was taken and to this mixture of polymers and methanol solution and drug was transferred. This mixture will be stirred for 15- 20minutes until the mixture was dissolved completely. Now this was transferred into a china dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from China dish and it was packed in polythene sachets and stored in cool and dry place.

Solid Dispersion of Drug: Polymer Ratio 1:1:2(F2) (PEG6000: PEG4000)

500 mgof PEG6000and 1 gm of PEG4000 was weighed and added to 10ml of methanol and stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beaker was taken and to this mixture of polymers and methanol solution and drug was transferred. This mixture will be stirred for 15-20minutes until the mixture was dissolved completely. Now this was transferred into a china dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from china dish and it was packed in polythene sachets and stored in cool and dry place.

Solid Dispersion of Drug: Polymer Ratio 1:1:3(F3) (PEG6000: PEG4000)

500mgof PEG6000and 1.5gm of PEG4000 was weighed and added to 10ml of methanol and

stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beacker was taken and to this mixture of polymers and methanol solution and drug was transferred. This mixture will be stirred for 15-20 minutes until the mixture was dissolved completely. Now this was transferred into a china dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from China dish and it was packed in polythene sachets and stored in cool and dry place.

Solid Dispersion of Drug: Polymer Ratio 1:1:4(F4) (PEG6000: PEG4000)

500mg of PEG6000 and 2gm of PEG 4000 was weighed and added to 10ml of methanol and stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beaker was taken and to this mixture of polymers and methanol solution and drug was transferred. The mixture will be stirred for 15-20minutes until the mixture was dissolved completely. Now this was transferred into a China dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from China dish and it was packed in polythene sachets and stored in cool and dry place.

Solid Dispersion of Drug: Polymer Ratio 1:1:5 (F5) (PEG6000: PEG4000)

500mg of PEG6000 and 2.5 gm of PEG 4000 was weighed and added to 10ml of methanol and stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beaker was taken and to this mixture of polymers and methanol solution and drug was transferred. The mixture will be stirred for 15-20minutes until the mixture was dissolved completely. Now this was transferred into a China dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from China dish and it was packed in polythene sachets and stored in cool and dry place.

Solid Dispersion of Drug: Polymer Ratio 1:1: 6 (F6) (PEG6000: PEG4000)

500mg of PEG6000 and 3 gm of PEG 4000 was weighed and added to 10ml of methanol and stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beaker was taken and to this mixture of polymers and methanol solution and drug was transferred. The mixture will be stirred for 15-20minutes until the mixture was dissolved completely. Now this was transferred into a china dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from china dish and it was packed in polythene sachets and stored in cool and dry place.

Solid Dispersion of Drug: Polymer Ratio 1:1:7 (F7) (PEG6000: PEG4000)

500mg of PEG6000 and 3.5 gm of PEG 4000 was weighed and added to 10ml of methanol and stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beaker was taken and to this mixture of polymers and methanol solution and drug was transferred. The mixture will be stirred for 15-20minutes until the mixture was dissolved completely. Now this was transferred into a china dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from china dish and it was packed in polythene sachets and stored in cool and dry place.

Solid Dispersion of Drug: Polymer Ratio 1:1:8 (F8) (PEG6000: PEG4000)

500mg of PEG-6000 and 4 gm of PEG-4000 was weighed and added to 10ml of methanol and stirred well for 2-3 minutes till it gets dissolved.50 mg of Lacidipine was weighed and kept aside. 100 ml beaker was taken and to this mixture of polymers and methanol solution and drug was transferred. The mixture will be stirred for 15-20minutes until the mixture was dissolved completely. Now this was transferred into a China dish and kept in an incubator at 45^0 c for one day until it was dried completely. After drying this content was removed from China dish and it was packed in polythene sachets and stored in cool and dry place.

Evaluation parameters for the solid dispersions for Lecidipine formulations

Drug Content:

The solid dispersion was taken in to a mortar and crushed the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved and made up to

volume with Phosphate buffer pH (7.0) with 0.5% SLS. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV- spectrophotometer at a by using Phosphate buffer pH (7.0) with 0.5% of SLS as blank.

In vitro drug release studies:

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of Phosphate buffer pH (7.0) with 0.5% of SLS as dissolution medium. Temperature of the dissolution medium was maintained at 37.5˚C, aliquot of dissolution medium(5ml) was withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 252 nm and concentration of the drug was determined from standard calibration curve.

Drug Kinetics studies: [19]

The invitro dissolution profile of all batches were fitted to Zero order, first order, Higuchi model and Koresmeyer-Peppas model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the above plot.

- **Zero-order kinetic model** – Cumulative % drug released Vs time.
- **First-order kinetic model** – log cumulative % drug remaining Vs time.
- **Higuchi model** - Cumulative % drug released Vs square root of time.
- **Korsmeyer-Peppas model** - log cumulative % drug released Vs log time.

S. No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

Table No.4. Release kinetics data

Stability Studies [20]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug products varies with time and the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest period for the drug substance or a shelf – life for the drug product and recommended storage conditions as per ICH guidelines. Stability studies on prepared solid dispersion containing best batch F1 was carried out by storing 1gm of solid dispersion placed in a desicater at room temperature for a period of 3 months. The solid dispersions visually examined for any physical change, drug release and drug content were estimated at the end of 3 months.

Table no:5 ICH Stability Studies guidelines

S.NO	Study	Storage Condition	Minimum Time Period
1.	Long term	25ºC± 2ºC/60 %RH± 5ºC (or) 30C±2ºC/ 65%RH±5%RH	12 months
2.	Intermediate	30ºC±2ºC/65%RH±5%RH	6months
3.	Accelerated	40ºC ±2ºC / 75% RH ±5 % RH	6months

3. Results and Discussion

PREFORMULATION STUDIES

1.1. Melting point by capillary tube method

Melting point of Lacidipine was observed for quality determination, it matches with standard value and the values are given in Table 9.1.

Drug	**Standard value**	**Experimental value**
Lacidipine	174.-175 ºC	175 ºC

Table 6 Melting point of pure drug

Drug-Excipient Compatibility Studies

Physical Compatibility Study

S.No	**Drug and Excipient**	**Initial**	**Description and condition**					
			At Room Temperature			**At 40 oC ±2o and 75 % RH ± 2% (in days)**		
			10	20	30	10	20	30
1	Lacidipine	White to off- white crystalline solid Powder	NC	NC	NC	NC	NC	NC
2	PEG 6000	White to off- white solid powder	NC	NC	NC	NC	NC	NC
3	PEG 4000	Creamy white waxy powder	NC	NC	NC	NC	NC	NC
5	Lacidipine +PEG 6000	White crystalline solid	NC	NC	NC	NC	NC	NC
6	Lacidipine + PEG 4000	White waxy powder	NC	NC	NC	NC	NC	NC
7	Lacidipine+ PEG 6000+ PEG 4000	Off white creamy wax powder	NC	NC	NC	NC	NC	NC

*NC-No Change

Table 7 Physical Compatibility of Drug and Excipients

Inference

The Physical compatibility study is shown in table 9.2. The drug and excipient were evaluated for 10, 20 and 30 days at room temperature and at 40˚C±2˚C/75±5% Relative Humidity. There was no change in colour.

Therefore, the drug and excipients are physically compatible with each other. The excipients which are compatible with the drug were selected for the formulation

UV Spectrum:

The UV spectrum if the Lacidipine was run with 200-400nm and the Absorption spectrum was obtained at 252 nm.

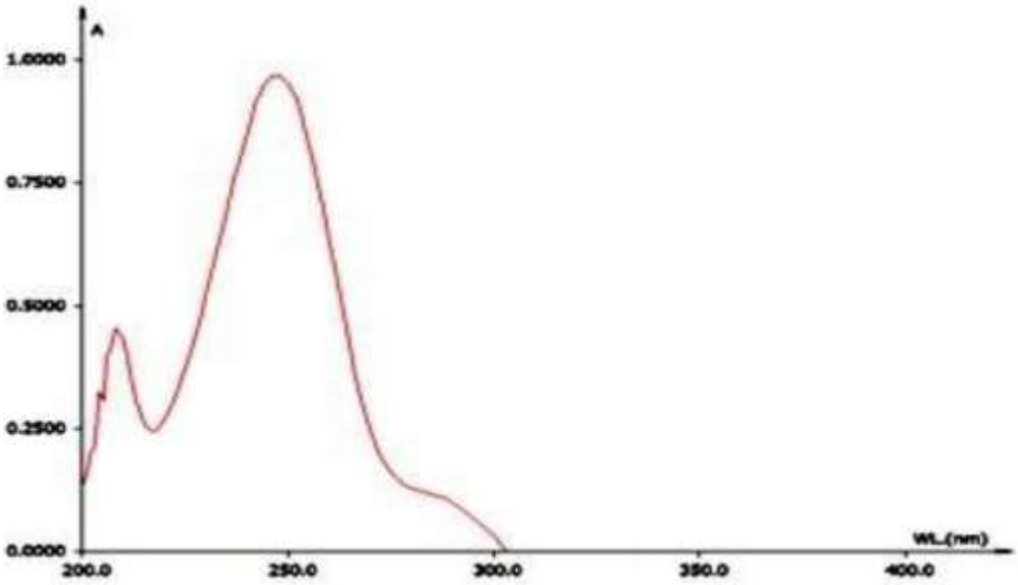

Figure2: The UV Spectrum for Lacidipine

Calibration curve for the Lacidipine

The standard calibration graph for the pure drug simvastatin had been carried out using pH 7.0 phosphate buffer. The linearity between the concentration and absorbance had been keenly observed, the value of linearity was found to be r^2= 0.992.the data were shown in the table no:8 and the graph was represented in the fig no:4.

S.No	Concentration (mg/ml)	Absorbance at 252 nM
1	0	0
2	0.5	0.162
3	1	0.359
4	1.5	0.561
5	2	0.778
6	2.5	0.979

Table 8 calibration curve values for Lacidipine

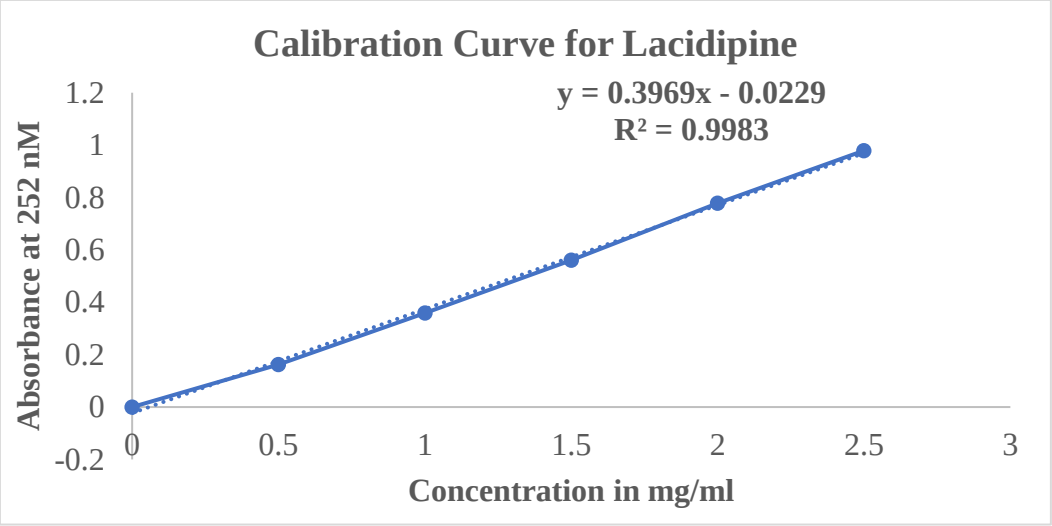

Figure 3 Calibration curve for Lacidipine

DRUG –POLYMER COMPATIBILITY STUDIES BY FTIR

The compatibility of the Polymer with the drug had been studied with the help of FTIR, DSC and XRD. The studied showed that there are compatible with each other and shows no significant change in the spectra.

FTIR STUDIES:

In the FTIR studies the IR peaks of the physical mixture had been compared with the individual excipient's were there were no shifts of peaks or appearance of the newer peaks compared with each other, which shows that they are chemically stable and compatible. the results are shown in the table no:9,10,11&12 and fig no:5,6,7&8.

IR spectra of Lacidipine pure drug, F1 Formulation illustrated in Table no: 9 & 12 Figure no:5 &8 Characteristic peaks of Lacidipine at 3550.31 cm^{-1} (O-H stretching), 3469.31 cm^{-1} (alcO-H stretching), 1011 cm^{-1} (C=O stretching), 1043 cm^{-1}(C-O-C bending), 1111.76cm^{-1}(C-O ether bending), were observed.

DSC studies:

The DSC thermogram of the drug in figure 5 depicts a sharp endothermic peak at 186°C corresponding to the melting temperature of lacidipine. Such sharp endothermic peak signifies that drug used was in pure crystalline state[36]. A complete disappearance of the drug melting peak was observed in the physical mixture of solid dispersion F1 as shown in figure 6 and 7 respectively, a fact that agrees with the drug was molecularly dispersed within the solid matrix and also indicate the formation of an amorphous solid mixture.

Drug Content

The Drug content of the Solid dispersion formulations of the Lacidipine of F1 and F8 were calculated. the formulation F1 was shows the 99.87 ± 0.012 than compare with the remaining formulations

S .no	Formulation	%Drug content
1	F1	99.87 ± 0.012
2	F2	98.97 ± 0.024
3	F3	96.98 ± 0.025
4	F4	98.41 ± 0.015
5	F5	97.47 ± 0.045
6	F6	97.14 ± 0.041
7	F7	98.01 ± 0.057
8	F8	96.52 ± 0.012

***Mean** ± SD of three values

Table 9: drug content of Lacidipine solid dispersion formulation F1 to F8

In vitro dissolution studies of the formulations F1 – F8

S.No	Time in min	% of Cumulative Dissolution Studies			
		F1	F2	F3	F4
1	0	0	0	0	0
2	5	16.12 ± 0.15	15.14 ± 0.45	13.52 ± 0.85	13.45 ± 0.54
3	10	24.15 ± 0.17	22.13 ± 0.23	21.15 ± 0.45	20.14 ± 0.25
4	20	36.15 ± 0.25	34.15 ± 0.24	33.15 ± 0.24	32.14 ± 0.47
5	30	46.17 ± 0.54	42.14 ± 0.15	41.12 ± 0.54	40.12 ± 0.54

6	40	54.84 ± 0.74	51.25 ± 0.25	50.14 ± 0.23	51.24 ± 0.74
7	60	66.17 ± 0.47	63.14 ± 0.15	62.13 ± 0.14	61.24 ± 0.45
8	90	75.12 ± 0.41	72.15 ± 0.85	71.25 ± 0.47	70.15 ± 0.65
9	120	82.14 ± 0.65	79.12 ± 0.45	78.15 ± 0.46	77.45 ± 0.45
10	130	91.14 ± 0.25	90.15 ± 0.45	91.24 ± 0.54	91.25 ± 0.25
11	140	99.87 ± 0.78	97.45 ± 0.14	95.14 ± 1.24	96.25 ± 0.25

Table 10 Invitro dissolution studies of Lacidipine formulation F1- F4

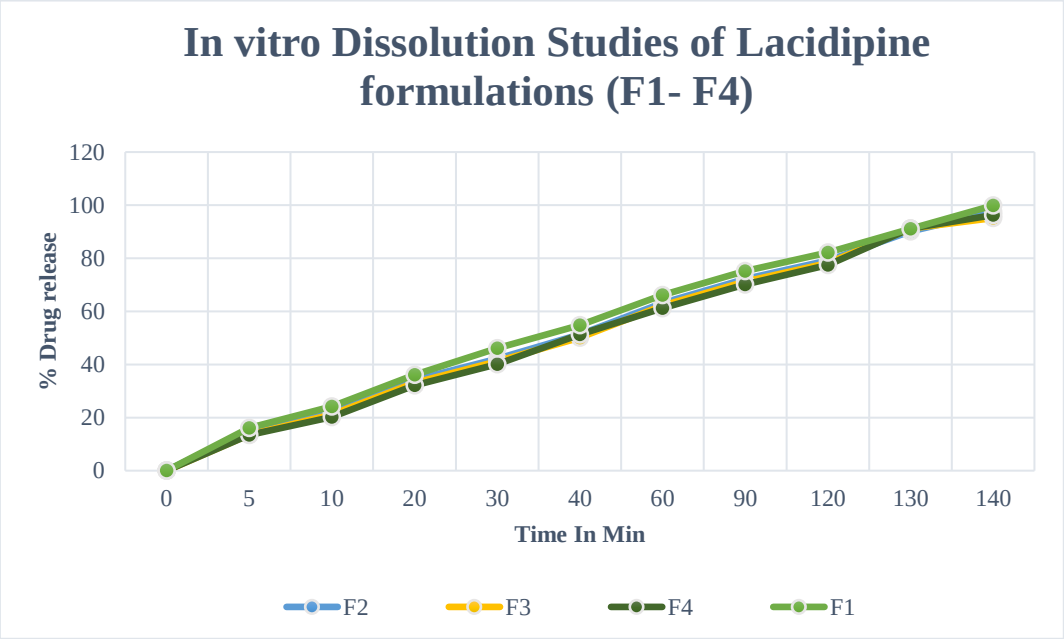

Figure 4 Graphical representation of Invitro dissolution studies of Lacidipine formulation F1-F4

Table 11 Invitro dissolution date of Lacidipine formulation F5- F8

S.No	Time in min	% of Cumulative Dissolution Studies			
		F5	F6	F7	F8
1	0	0	0	0	0
2	5	12.56 ± 0.54	12.17 ± 0.85	12.85 ± 0.54	13.54 ± 0.41
3	10	18.25 ± 0.74	17.54 ± 0.78	18.65 ± 0.24	19.15 ± 0.28
4	20	31.25 ± 0.12	32.45 ± 0.87	30.25 ± 0.56	32.25 ± 0.75
5	30	39.14 ± 0.45	41.15 ± 0.54	43.25 ± 0.15	44.12 ± 0.54
6	40	50.24 ± 0.25	51.24 ± 0.54	53.45 ± 0.56	52. 24 ±0.24
7	60	60.12 ± 0.85	61.25 ± 0.54	62.15 ± 0.65	61.25 ± 0.24
8	90	70.15 ± 0.45	72.54 ± 0.47	73.45 ± 0.68	73.15 ± 0.56
9	120	76.45 ± 0.87	80.15 ± 0.85	80.12 ± 0.75	80.14 ± 0.74
10	130	82.74 ± 0.47	89.12 ± 0.63	89.88 ± 0.57	88.14 ± 0.54
11	140	95.48 ± 0.56	96.42 ± 0.54	95.89 ± 0.85	96.14 ± 0.74

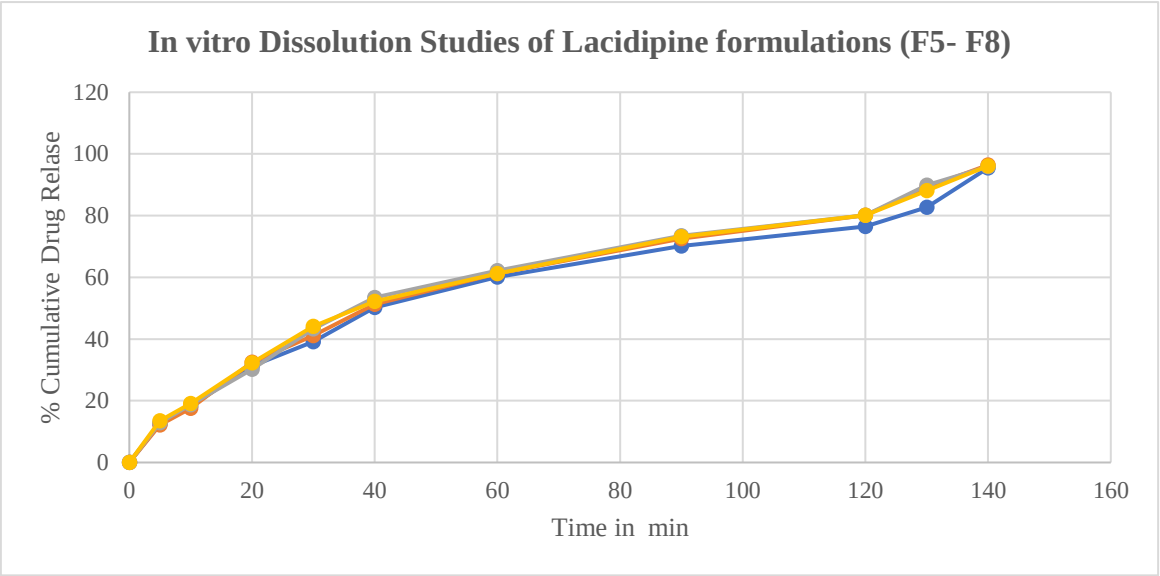

Figure 5 In vitro Drug release of the Formulations F5 to F8

The Formulations F1 and F8 were evaluated for the % Drug release using the Dissolution apparatus and sample from the dissolution were collected in time interval of 0 to 140 min, the sample was estimated UV spectroscopy at 252 nm. and the % drug release were tabulated. The formulations F1 and F8 shows the vales were ranging from to the 12.17 to the 99.87. The formulation F1 gives the % Drug release at 140 min as 99.87 ± 0.78 and the F2 formulations gives the values ranging from 97.45 ± 0.14 respectively.

Table 12 Comparative study of the % Drug release of the optimized formulation F1 , Pure drug the marketed formulation

Time (min)	**% Drug release of (F1)**	**% Drug release of pure drug**	**% Drug release of Marketed product**
0	0	0	0
5	16.12 ± 0.15	11.26±0.25	15.42±0.65
10	24.15 ± 0.17	19.21±0.54	21.25±0.78
20	36.15 ± 0.25	33.21±0.54	34.15±0.45
30	46.17 ± 0.54	41.52±.024	45.12±0.56
40	54.84 ± 0.74	53.01±1.24	53.18±0.78
60	66.17 ± 0.47	62.34±0.12	64.85±0.89
90	75.12 ± 0.41	70.12±0.14	72.65±0.87
120	82.14 ± 0.65	79.54±0.58	81.57±0.78
130	91.14 ± 0.25	89.54±0.45	90.87±0.54
140	99.87 ± 0.78	96.82±0.47	98.12±0.12

The % drug release of the formulation F1 Shows the good drug release rate compare with pure drug and marketed formulation (Lacivas ® Sun Pharmaceutical Industries Ltd) the results were tabulated. the % drug release of the F1 formulation give 99.87 ± 0.78 .

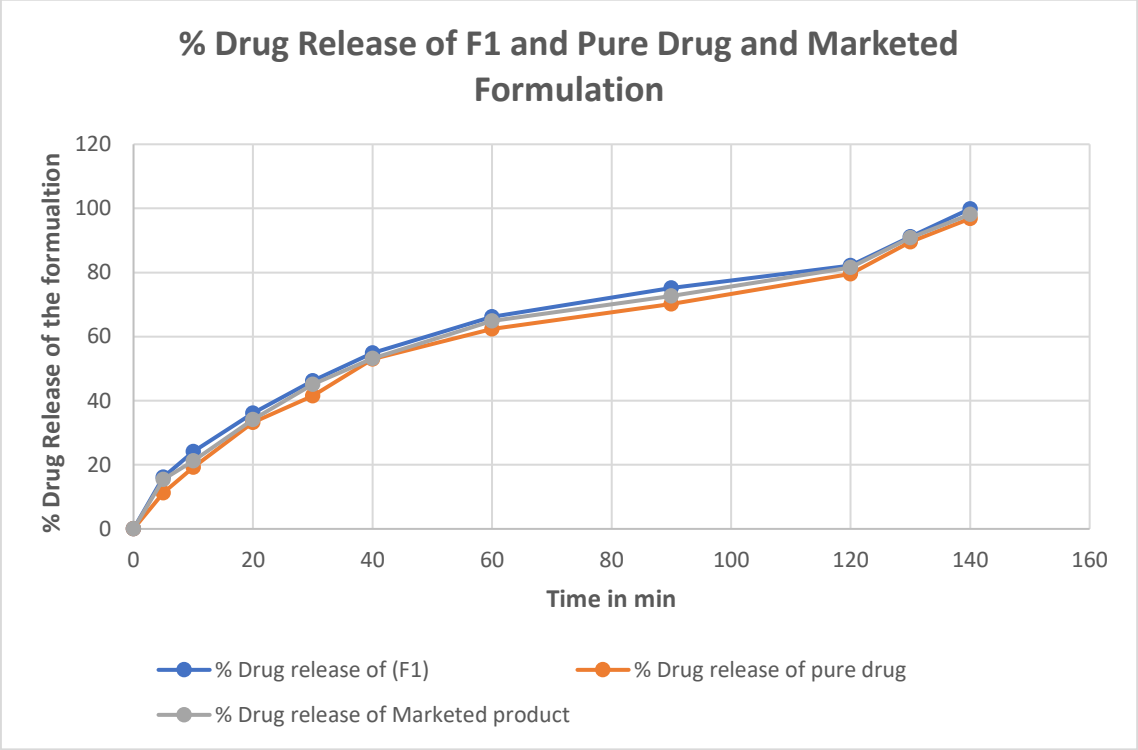

Figure 6: % Drug Release of F1 and Pure Drug and Marketed Formulation Drug Kinetis studies of formulation F1

Table13 Drug kinetic studies of optimised formulation F1

Time (min)	**cumulative % drug released**	**% drug remaining**	**Square root time**	**log Cumu % drug remaining**	**log time**	**log Cumu % drug released**	**% Drug released**	**Cube Root of % drug Remaining (Wt)**	**Wo-Wt**
0	0	100	0.000	0.000	0.000	0.000	100	4.642	0.000
5	16.12	83.88	2.236	1.924	0.699	1.207	16.12	4.377	0.265
10	24.15	75.85	3.162	1.880	1.000	1.383	8.03	4.233	0.409
20	36.15	63.85	4.472	1.805	1.301	1.558	12	3.997	0.645
30	46.17	53.83	5.477	1.731	1.477	1.664	10.02	3.776	0.866
40	54.84	45.16	6.325	1.655	1.602	1.739	8.67	3.561	1.081
60	66.17	33.83	7.746	1.529	1.778	1.821	11.33	3.234	1.408
90	75.12	24.88	9.487	1.396	1.954	1.876	8.95	2.919	1.723
120	82.14	17.86	10.954	1.252	2.079	1.915	7.02	2.614	2.028
130	91.14	8.86	11.402	0.947	2.114	1.960	9	2.069	2.573
140	99.87	0.13	11.832	-0.886	2.146	1.999	8.73	0.507	4.135

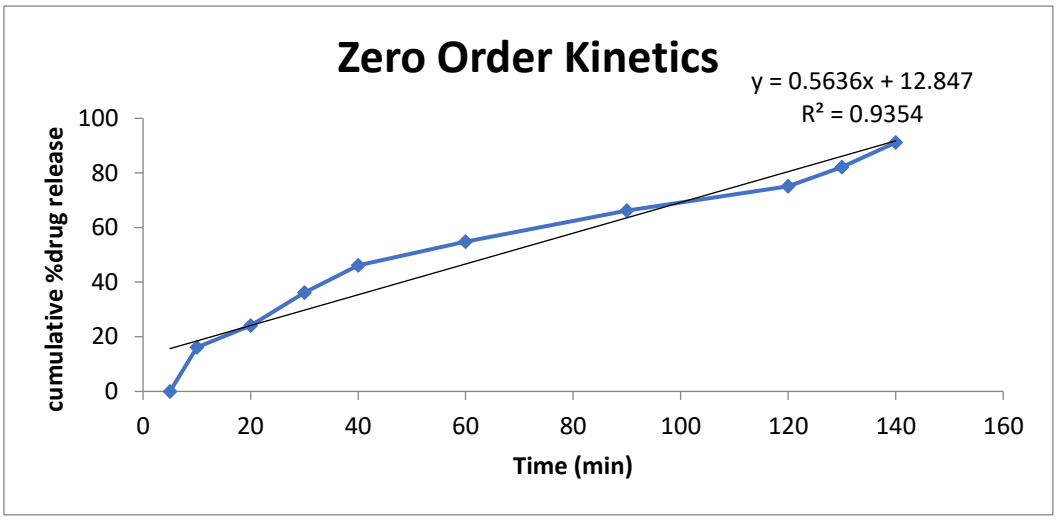

Figure 7 Zero Order Kinetics of the Formulation F1

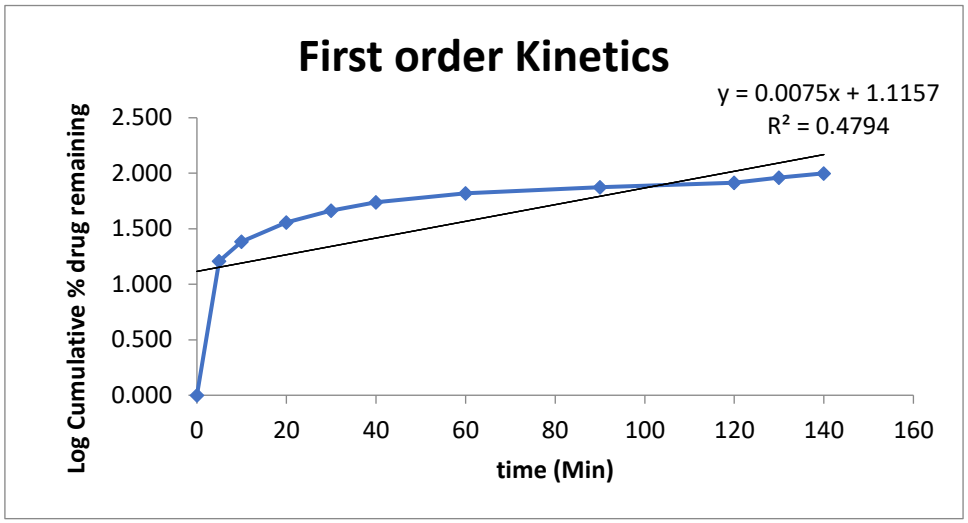

Figure 8 First Order Kinetics of the Formulation F1

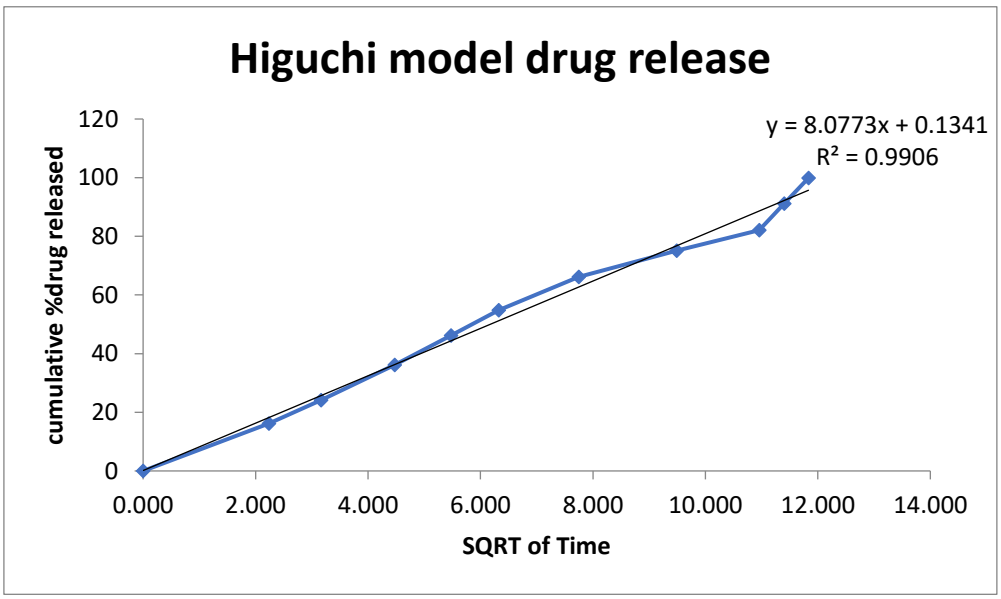

Figure 9 Higuchi Model formulation F1

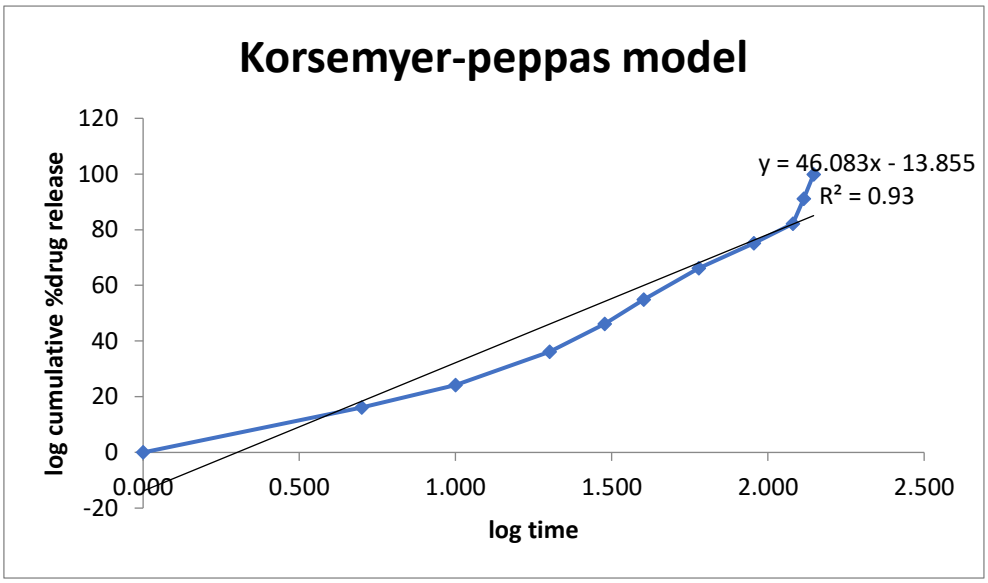

Figure 10 Kores-Peppas Model formulation F1

Table 14regression values of Lecidipine drug kinetic studies

Order of kinetics	**Zero order**	**First order**	**Higuchi plot**	**Kors-peppas Model**
Regression value(r2)	0.9354	0.4794	0.9906	0.930

The drug kinetic studies of the formulation F1 follows The Higuchi model is a mathematical model that describes the rate of drug release from an insoluble polymer matrix. It is based on Fickian diffusion and suggests that drug release occurs through diffusion through dispersed vesicles.

Table 15 Stability studies of the optimised formulation F1

S.no.	**Characteristics**	**Initial**	**At the end of 1 month**	**At the end of 2 month**	**At the end of 3 month**
1	Physical appearance	White	No Change	No Change	No Change
2	Drug content (%)	99.87%	98.87%	96.75%	94.89%
3	Drug Release at end of 120 min	78.98%	75.54%	73.45%	71.02%

The Accelerated stability studies were carried out as per the ICH Guidelines, (40ºC ±2ºC / 75% RH ± 5 % RH) at the end of 3rd month, the formulation F1 shows no significant change Physical and chemical characteristics of the solid dispersion of the Lacidipine. At the end of 3rd month. The % drug content 94.89 % and In vitro drug release at 120 min was found to be 71.02 %.

4. Discussion

The oral drug delivery is the most prominent, simplest and easiest way of administration of drug. It is estimated that 40 %of new chemical entities being discovered are poorly water soluble. Therefore, enhancement of the solubility is the part of the strategy to improve its bioavailability. Many techniques were used to improve the solubility of the drugs. The aim of works is the enhancement of the solubility of Lacidipine by using of solid dispersion using the solvent evaporating technique. The Preformulation were performed for the Lacidipine like Melting point found to be 175 ºC. The drug and excipient were evaluated for 10, 20 and 30 days at room temperature and at 40˚C±2˚C/75±5% Relative Humidity. There was no change in colour. Therefore, the drug and excipients are physically compatible with each other. The excipients which are compatible with the drug were selected for the formulation. The UV spectrum if the Lacidipine was run with 200-400nm and the Absorption spectrum was obtained at 252 nm. The standard calibration graph for the pure drug simvastatin had been carried out using pH 7.0 phosphate buffer. The linearity between the concentration and absorbance had been keenly observed, the value of linearity was found to be r^2= 0.9983. The compatibility of the Polymer with the drug had been studied with the help of FTIR, DSC and XRD. The studied showed that there are compatible with each other and shows no significant change in the spectra. IR spectra of Lacidipine pure drug, F1 Formulation Shows Characteristic peaks of Lacidipine at 3550.31 cm^{-1} (O-H stretching), 3469.31 cm^{-1} (alcO-H stretching), 1011 cm^{-1} (C=O stretching), 1043 cm^{-1}(C-O-C bending), 1111.76cm^{-1}(C-O ether bending), were observed. The DSC thermogram of the drug in figure 5 depicts a sharp endothermic peak at 186°C corresponding to the melting temperature of lacidipine. Such sharp endothermic peak signifies that drug used was in pure crystalline state. A complete disappearance of the drug melting peak was observed in the physical mixture of solid dispersion F1, a fact that agrees with the drug was molecularly dispersed within the solid matrix and also indicate the formation of an amorphous solid mixture. Crystallinity is indicated by the presence of sharp peaks that are absent in the case of amorphous drugs. In X-ray diffractogram, LCDP shows characteristic peaks at 8.15º, 12.15 º, 18.54 º, 19.75 º, 21.15 º, 22.14 º, 24.12 º, 30.13 º ,33.35 º. The Drug content of the Solid dispersion formulations of the Lacidipine of F1 and F8 were calculated. the formulation F1 was shows the 99.87 ± 0.78 than compare with the remaining formulations. The Formulations F1 and F8 were evaluated for the % Drug release using the Dissolution apparatus and sample from the dissolution were collected in time interval of 0 to 140 min, the sample was estimated UV spectroscopy at 252 nm. and the % drug release were tabulated. The formulations F1 and F8 shows the vales were ranging from to the 12.17 to 99.87 . The formulation F1 gives the % Drug release at 120 min as 99.85 ± 0.78 and the F2 formulations gives the values ranging from 97.85 ± 0.84 respectively. The drug kinetic studies of the formulation F1 follows The Higuchi model is a mathematical model that describes the rate of drug release from an insoluble polymer matrix. It is based on Fickian diffusion and suggests that drug release occurs through diffusion through dispersed vesiclesThe Accelerated stability studies were carried out as per the Ich Guidelines, (40ºC ±2ºC / 75% RH ± 5 % RH) at the end of 3rd month, the formulation F1 shows no significant change Physical and chemical characteristics of the solid dispersion of the Lacidipine. At the end of 3rd month. The % drug content 94.89 % and In vitro drug release at 120 min was found to be 71.02 %.

5. Conclusion

The present study was aimed in developing the solid dispersion studies of combination of the polymers like PEG 6000: PEG 4000 prepared by solvent evaporation technique with ratio of Drug and polymer ratio was 1:1:1. The Lacidipine solid dispersion were evaluated for

physicochemical characteristics like drug content and in vitro drug release studies. Form FTIR studies, it concluded that there was no chemical interaction between the drugs and polymers like PEG 6000 and PEG 4000. it can provide promising way to enhance its solubility and dissolution rate. The compatibility of the drug and excipients was confirmed by DSV and XRD analysis which clearly compatibility of the polymer and drug. The optimized formulation F1 was Compared with the marketed formulation the F1 shows the In vitro drug release at 99.87% at 140 min. based on the mathematical models, the concluded that formulation F1, the regression value found to be 0.9906 fitted with Higuchi model follows Fickian diffusion and suggests that drug release occurs through diffusion through dispersed vesicles.

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