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Solubility and Dissolution Enhancement of Erlotinib by Liquisolid Compact Technique

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Abstract-

In this study we try to increase the dissolution power of drug Erlotinib (Anti-Cancer drug) which is poorly soluble in nature) by using very famous technique called liquisolid compact method. In preparation of liquisolid tablet of Erlotinib using liquid vehicle polyethylene glycol 400(PEG 400) which is non-volatile in nature. We use Avicel PH200 used as carrier material, and for coating we used Aerosil 200 in different ratios. Mathematical model and 3^2 full factorial design became useful in formulation of different powder system. We evaluated our preparation by their micrometric properties, FTIR study(for showing interaction between drug and excipients), DSC study and XRD study(for showing crystalline structure of drug).For optimization Response surface methodology (3^2 factorial) was working to learning the cause of independent variables like drug concentration in liquid medication (X_1) and carrier and coating ratio (R) (X_2) on the dependent variables like Cumulative % drug release at 15 min (Y_1) and Angle of slide (Y_2). Based on this result, formulation O1 at level 0 (20) for X_1 and level 0 (25) for X_2 was selected as optimized formulation. Data was analyzed by using ANOVA, and value of $P<0.05$ was found to constant, it's very important. In vitro dissolution of formulation was studies and compare with marketed formulation, in result liquisolid tablets shows higher % of dissolution due to high wetting properties due to using of MCC. We also evaluated its stability studies at $40^0C \pm 2^0C$ temperature and 75 ± 5% RH for one month (accelerated stability study) which showed no major change in percentage drug content and its release patent. All result shows our formulation which main goal is increase dissolution of erlotinib was successfully formulated.

Key Words: Erlotinib, solubility enhancement, 3^2factorial design, liquisolid compact.

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Introduction

In current situation too many drugs which are poorly or very less soluble in water, due to their low solubility their bioavability, absorption rate and dissolution power decrease. If orally administered drug have low water solubility so it became challenging to formulate because of its solubility. Solubility of drug directly affect the its bioavability, if bioavability is low so dose is increases and also side effects are increases of formulation. Presently everyday new molecules are available for treatment of various diseases, but almost more than 50% are poorly water soluble, so it's great need to prevent this factor. If we increase the drug water solubility, so we can achieve maximum bioavability and reduce its toxic effects. (Thakkar, et al., 2010) (Brahmankar, et al., 2003; Varandal, et al., 2013).

Our goal of current study is increase the solubility and improves dissolution profile of poorly water soluble anticancer drug erlotinib by using Liquisolid compact technique in which we use various carrier material and different coating materials with various loading factor and excipients ratio and various liquid vehicles which are non-volatile in nature. Erlotinib is anti-cancer drug and use into breast cancer. It is solid powder and very slightly soluble in water (www.drugbank.ca/drugs/db00530).

Material and Method

Chemical and Instruments

API Erlotinib is kindly gifted by Khandelwal Laboratories. Pvt. Ltd. Non-Volatile solvents like PEG-200, Glycerine, PEG-400, Tween-80, Tween-20, Propylene Glycols etc. are gifted by Regent chemicals, Mumbai. Carrier materials like Avicel PH 102, Avicel PH 200, lactose etc. from Signet Chemicals, Mumbai. Coating material like Aerosil 200, silica (Cab-o-sil) etc. from Signet Chemicals, Mumbai. Disintegrants like Sodium Starch Glycolate, Croscarmellose Sodium etc. provided by Apple Pharma/Ascot Pharma. All chemicals were analytical grade used. A Digital weight balance (K. Roy Swisser), Compression machine (Hardik Engineering works), Hardness Tester-Pfizer (Shital scientific industry), Friabilator (Kumar Engineering), Sonicator (120-W, PCI, Mumbai), Tap densitometer (Electro lab, Mumbai), Dissolution apparatus-USP Type II (Electrolab), UV-Visible double beam spectrophotometer (Model no-1800 Shimadzu, Japan), FTIR Spectrophotometer (Perkin Elmer model spectrum BX-II, USA), Disintegration test apparatus (Electro lab, Mumbai) and Melting point apparatus (VMP-D, veego Pvt. Ltd., Mumbai) were used in study.

Preformulation Studies and Analytical Method

Did as described by Kasture, et al., (2011); Sravana, et al., (2012); Izhar, et al., (2012); Chella, et al., (2012) and Vaskula, et al., (2012) were used.

Melting point

Erlotinib's melting point was evaluated using very popular capillary tube method.

UV Spectroscopy (Determination of λmax)

Drug weighed (100mg) and transferred to 100ml flask, dissolve in 100ml methnol. Solution was diluted suitably and analyzed at 333nm

FT-IR spectroscopic study

Sample preparation by mixing the drug with KBr and scanned between frequency ranges 4000-450 cm^{-1}.

Flow Characteristics

Determination of angle of repose, Carr's index and Hausner's ratio, BD, TD, etc.

Drug-excipients compatibility study

The compatibility study of the drugs and excipients was checked out using the FTIR. For Erlotinib, Erlotinib+PEG400, Erlotinib+Avicel PH 200, Erlotinib+Aerosil200, Erlotinib+ SSG and Erlotinib+PEG400+AvicelPH200+Aerosil200+ SSG were studied separately.

Calibration curve of Erlotinib in methanol

Standard stock solution preparation

100 mg (0.1gm) of Erlotinib dissolved in methyl alcohol and then volume was make-up to 100 ml with methanol so became a standard stock solution which concentration is 1000µg/ml of Erlotinib.

Working sample solutions preparation

Dilute 10ml of standard stock solution with 100 ml methanol to get 100 µg/ml solution. Take 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml and 3 ml solution and transfer in 10ml volumetric flask and fill upto mark to get 10, 15, 20, 25 and 30 µg/ml working sample solutions.

Scanning of solution in UV-Visible spectrophotometer

Take absorbance all prepared solution at 333 nm using UV-Visible spectrophotometer.

Calibration curve of Erlotinib in 0.1N HCl containing 1% SDS solution

Stock solution preparation- 100 mg(0.1gm) of Erlotinib was dissolved and make-up volume upto 100 ml with 0.1N HCl containing 1% SDS so we get a stock solution which is 1000 µg/ml in concentration of Erlotinib.

Working sample solutions preparation-

Dilute 10 ml stock solution with 100 ml 0.1N HCl having 1% SDS so we get 100 µg/ml solution, accurately measure and transfer (1, 3, 5, 7, 9 and 11 ml) in 10 ml volumetric flasks and dilute with 0.1N HCl containing 1% SDS to get 10, 30, 50, 70, 90 and 110 µg/ml.

Scanning of solution in UV-Visible spectrophotometer

Taking absorbance of solutions at 340 nm using UV-Visible spectrophotometer. 0.1N HCl contain 1% SDS set as blank.

Solubility studies

The Erlotinib's solubility was carried out in Water, Propylene Glycol (PG), Polyethylene Glycol 400 (PEG 400), Glycerine, Span 80 and Tween 80. When we added excess amount of drug in solvent to form saturated solution and shacked for 2 days at 25°C in shaker. After filtering the supernatant was again diluted with methanol and analyze with UV-Visible Spectrophotometer at 333 nm. Erlotinib's solubility in various liquid vehicle was calculated using calibration curve method.

Preparation of Liquisolid compacts

As per method described by Thakkar, et al (2010), Kasture, et al (2011), Sravana, et al (2012), Izhar, et al., (2012), Chella, et al., (2012) and Vaskula, et al., (2012).

Application of the mathematical model for designing the Liquisolid System

In current study, liquid vehicle like PEG-400, as a carrier Avicel PH 200 and as a coating material (which improves flow properties) we used Aerosil 200. Carrier coating ratio or excipients ratio was calculated by equation; **R =Q/q** (Where R = Carrier coating ratio, Q = Coating, q = Carrier material).

Liquid load factor (Lf) is a ratio of liquid medication (W) and carrier powder (Q) **Lf = W/Q**

For calculation of amount of each ingredient we used Flowable liquid retention potentials (Φ -values). Its relation with R is show in equation. **Lf = Φca +Φco (1/R)**. Φco and Φca are the coating and carrier material's Φ value.

Calculation for Φ Value for Carrier material (Avicel PH 200)

Carrier is accurately weighed and kept at one of a Glass/metal plate with a refined surface and it is slowly raised till the plate becomes angular to the horizontal so that powder is about to slide. The angle at which powder slips was taken as angle of slide. It was used to measure the flow properties of powders.

Step-I **Step-II** **Step-III**

Fig.1: Angle of Slide Measurement

Preparation of Liquisolid Compacts

Exact quantity of drug was dissolved in Polyethylene glycol 400 (non-volatile solvent). After added an exact amount of coating and carrier material in liquid in mortar by continuously mixing. Then added sodium starch glycolate (disintegrant) and remaining ingredient in exact amount and mixed for 10-15 minutes in mortar. Lastly a final mixture compressed into tablets.

Formulation of preliminary trial batches for selection of R (carrier coating ratio)

Review of literature suggests minimum R (R_{min}) to be 20 (To maintain compressibility)

Formulation of preliminary batches for selection of % C_d

Evaluation for preliminary trial batch of Erlotinib liquisolid compacts.

Powder blend were evaluated for flow properties, Drug content, Angle of slide,In vitro drug release.

Evaluation of Liquisolid compact (Kasture SV et al 2011) (Sravana L et al 2012) (Izhar A S et al 2012) (Chella N et al 2012) (Vaskula S et al 2012)

Pre-compression parameter of formulation

Powder preparation was evaluated for flow properties

Drug content

10 mg of erlotinib taken in 10 ml flask containing methyl alcohol. 1 ml of this solution was diluted to 10 ml with methyl alcohol and absorbance of resulting solution was measured at λ_{max} of 333nm using methanol as blank.

Drug-excipients compatibility study by FTIR.

Drug and excipients (1:1) taken and kept for 30 days (40ºC/75% RH). Moisture free mixture and KBr in ratio 1:5 and triturate in mortar pestle. Then pure KBr use as a blank and all mixture scanned at 4000-450 cm^{-1}.

Differential scanning calorimetry (DSC) analysis

Each sample weighted 2-5mg and place into machine's aluminum coated pans. DSC of all the samples was scanned from 200C-3000C.

Percentage Yield

% yield of liquisolid compacts was calculated by this equation. % yield = (Practical mass / Theoretical mass) X 100.

Post-compression parameter of formulation

Test for Weight variation, Hardness, Friability etc

***In Vitro* Drug Release**

We used USP type II apparatus for this purpose. 900 ml 0.1N HCl containing 1% SDS as a dissolution medium. Temperature is maintained to 37 ± 0.5°C, rpm was 75. 5 ml test sample taken out at time gap and each time filled 5 ml fresh dissolution medium. sample filtered and properly diluted. Absorbance at

340nm measured by UV-Visible spectrophotometer.

Optimization by using 3^2 full factorial experimental design

For understanding of complexity of various formulations need a tool like factorial design. As per this concept number of experiments for study and independent variables are correlated with each other and its showing in equation form; Y= b0 +b1X1 + b2X2+b12X1X2 +b11X12+b22X2.

Where;

Y = dependent variable, b_0 = arithmetic mean response for 9 runs the number of experiments required for these studies is dependent on the number of independent variables selected, b_1 = estimated coefficient for X_1, b_2 = estimated coefficient for X_2.A 3^2 full factorial design is useful to study the effect of independent variables (Drug concentration in liquid medication (X_1), carrier coating ratio (X_2) on dependent variables (cumulative % drug release at 15 min (Y_1) ,Angle of slide (Y_2).

Table 2: Formulation of Factorial Batches

Sr No.	Cd (%)	R	L_f	W (mg)	Carrier(Q)=W/L_f (Avicel 102) (mg)	Coating(q)=Q/R (Areosil200) (mg)	5% Disintigrant (SSG) (mg)	Total weight (mg)
F1	15	20	0.563	166.66	296.02	14.801	23.87	501.35
F2	20	20	0.563	125.00	222.02	11.101	17.90	376.02
F3	25	20	0.563	100.00	177.62	08.881	14.32	300.82
F4	15	25	0.530	166.66	314.34	12.574	24.67	518.24
F5	20	25	0.530	125.00	135.84	09.400	18.51	388.75
F6	25	25	0.530	100.00	188.67	07.547	14.811	311.02
F7	15	30	0.509	166.66	327.42	10.910	25.25	530.24
F8	20	30	0.509	125.00	245.58	08.186	18.93	397.69
F9	25	30	0.509	100.00	196.46	06.549	15.15	318.16

Data analysis and model validation

For data analysis and model validation ANOVA used, which is generated by Design Expert 8.0.4.1. In this one center point generated which is based on total 9 runs. For using of ANOVA select a two checkpoint formulation.

Contour Plot and Surface Plot of Design

Here contour and surface plot design in expert 8.0.4.1 software.

Accelerated Stability Studies

Take a formulation sample, wrap in aluminum foil and place in accelerated stability chamber which temperature was 40 ± 2°C and relative humidity (RH) was 75 ± 5 %. Sample placed for 30 days **(**Sravana, et al., 2012; Izhar, et al., 2012).

Results and Discussion

Melting Point

Melting point of pure erlotinib was found in range 224-229°C.

Physical Appearance

All units are uniform and free form cracks and minor pinholes, Clear surface, Texture was good, color and surface was uniform in all.

Table 3: Characteristic of Drug Powder

Parameters	Result
Angle of Repose	38.03± 1.02°
Bulk Density	0.33 ± 0.02 gm/ml
Tapped Density	0.38 ± 0.05 gm/ml
Carr's Index	13.38 %
Hausner's Ratio	1.15

Table 4: Calibration curve of Erlotinib in Methanol &0.1N HCl Containing 1% SDS

In Methanol		In 0.1N HCl Containing 1% SDS	
Conc.(µg/ml)	**Absorbance**	**Conc. (µg/ml)**	**Absorbance**
0	0	0	0
5	0.161±0.003	10	0.101±0.002
10	0.325±0.002	30	0.325±0.017
15	0.432±0.001	50	0.506±0.007
20	0.552±0.002	70	0.590±0.004
25	0.733±0.004	90	0.731±0.005
30	0.824±0.003	110	0.888±0.004

Selection of Wavelength Maxima

A representative spectrum of Erlotinib shows wavelength maximum at 333 nm in methanol for concentration of 30µg/ml. Spectra is shown in Fig. 2 and 340 nm in for 0.1N HCl containing 1% SDS concentration of 110µg/ml. Spectra is shown in Fig. 3

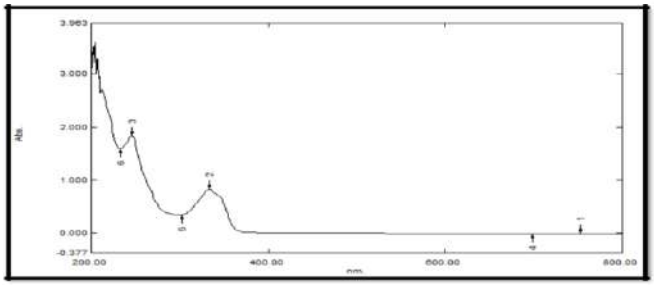

Fig. 2: Wavelength Maxima of Erlotinib in Methanol

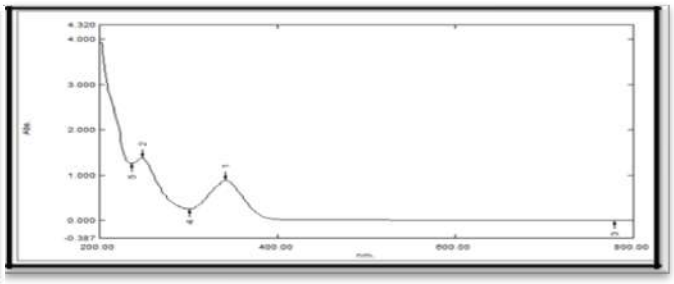

Fig.3 : Wavelength Maxima of Erlotinib in 0.1N HCl Containing 1% SDS

Drug-Excipients Compatibility Studies by FTIR

IR spectra of Erlotinib shown in Fig 4 and spectra with excipients are shown in Fig. 5 – 9 On the basis of observed spectrum we can say no interaction between drug and excipients.

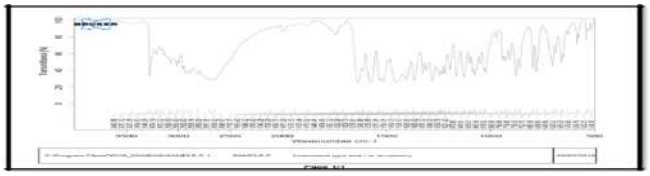

Fig.4 : FTIR Spectra of Drug Erlotinib

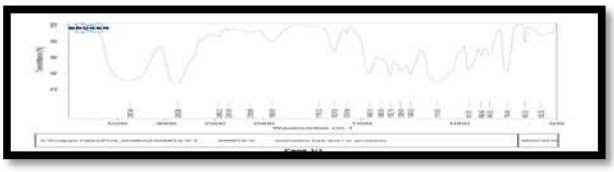

Fig.5 : FTIR Spectra of Drug+ PEG400

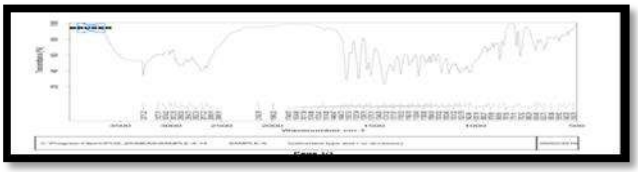

Fig 6: FTIR Spectra of Drug+ Avicel PH 200

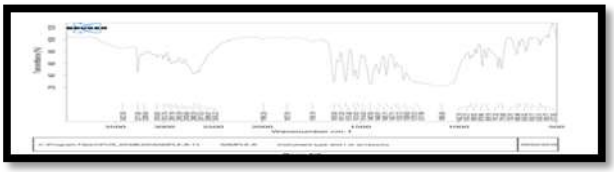

Fig 7: FTIR Spectra of Drug+ Aerosil 200

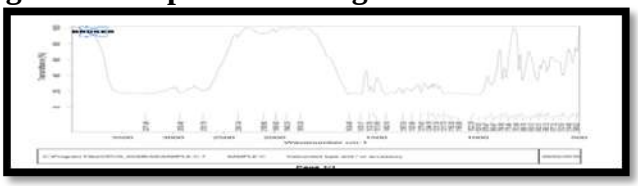

Fig 8: FTIR Spectra of Drug+ SSG

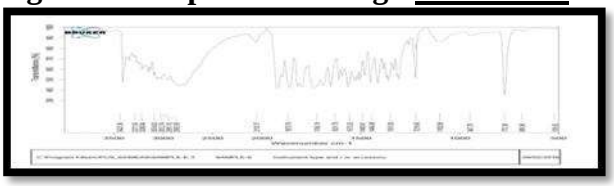

Fig 9: FTIR Spectra of Drug+ PEG400 +Aerosil 200 +Avicel PH200

Table 5: Solubility Study of Erlotinib In Different Organic Solvents

Solvent	Solubility mg/ml)
Water	0.00891± 0.0013
Proypylene Glycol	38.32± 3.65
Polyethylene Gylcol 400	300.78 ± 3.65
Glycerine	73.36 ±1.43
Span 80	80.65±2.12
Tween 80	61.05 ± 1.39

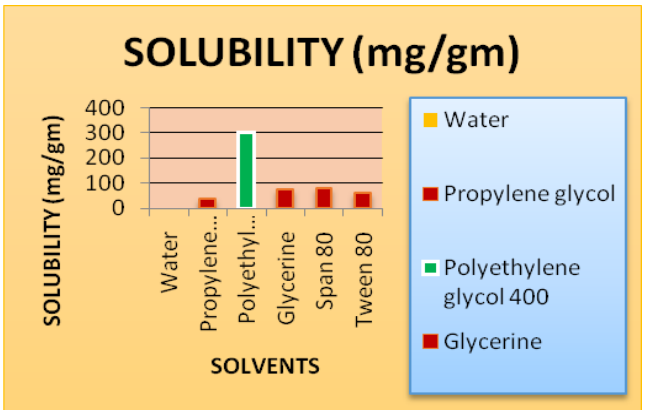

Fig 10: Solubility of Erlotinib in different solvent

Solubility Study

As shown in Table 5 the saturation solubility of Erlotinib in different solvent decreased in the order of;

PEG 400 >Span80>Glycerine>Tween 80> Propylene glycol > Water. Solubility of Erlotinib maximum was found in presence of PEG400 i.e. 300.78 (mg/gm).

Evaluation for Preliminary Trial Batch of Erlotinib Liquisolid Compacts

Angle of slide

Angle of slide indicates flow property of compact. As carrier coating ratio increases, angle of slide increases which indicates poor flow property, these batches were used further for optimization.

In-vitro drug release

In-vitro drug release study of trial batches, It was observed as drug concentration increased, drug release decreases.

Evaluation of Factorial Batches (F1 to F9)

Drug content Analysis- Drug content was found between 97.28 ± 2.31 to 101.25 ± 1.75**.**

Table 6: Drug Content of Factorial Batches (F1 to F9)

Batch No	Drug Content (%)	Batch No	Drug Content (%)
F1	97.28 ± 2.31	F6	99.16 ± 3.38
F2	101.25 ± 1.75	F7	98.19 ± 2.58
F3	98.48 ± 1.25	F8	100.31 ± 1.08
F4	98.22 ± 1.70	F9	98.08 ± 2.14
F5	100.23 ± 1.98		

Evaluation of Powder Blend of Liquisolid Compact

Powder blend were evaluated for pre-compression parameters. As shown Table 7 the angle of slide of factorial batches was in the ranges from 27.33 to 34.00 which indicate the F1 to F3 batches had good flow property and F4 to F9 batches flow property was passable. The value of Carr's index indicates the compressibility of batches. The value of F1-F3 was found between 11.36 to 26.82 which indicate the show good compressibility and F4 to F9 had passable compressibility. The value of Hausner's ratio indicates acceptable compressibility.

Table 7: Pre-Compression Parameter of Formulation

Batch Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index(%)	Hausner's Ratio	Angle of Slide(°)
F1	0.40 ± 0.03	0.46 ± 0.01	13.04	1.15	28.00 ± 1.00
F2	0.39 ± 0.05	0.44 ± 0.03	11.36	1.12	29.00 ± 1.00
F3	0.39 ± 0.02	0.45 ± 0.02	13.33	1.15	27.33 ± 0.57
F4	0.31 ± 0.04	0.41 ± 0.03	24.39	1.32	33.62 ± 0.57
F5	0.31 ± 0.01	0.42 ± 0.02	26.19	1.35	32.30 ± 0.57
F6	0.32 ± 0.04	0.40 ± 0.02	20.00	1.25	31.56 ± 0.57
F7	0.31 ± 0.03	0.40 ± 0.03	22.50	1.29	34.00 ± 1.00
F8	0.30 ± 0.01	0.41 ± 0.02	26.82	1.36	33.66 ± 1.57
F9	0.31 ± 0.03	0.41 ± 0.04	24.39	1.32	33.00 ± 1.00

Table: 8 Cumulative % Drug Release of Erlotinib Liquisolid Compact

Time (min)	% Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	23.08 ± 1.32	22.06 ± 1.18	12.08 ± 1.24	26.10 ± 1.24	25.40 ± 1.30	14.54 ± 0.24	30.94 ± 1.64	33.78 ± 1.93	16.40 ± 1.44
10	40.04 ± 2.62	38.1 ± 1.74	34.47 ± 1.26	38.85 ± 1.51	36.02 ± 2.26	40.65 ± 2.10	50.28 ± 2.14	48.60 ± 1.56	37.27 ± 1.88
15	78.28 ± 1.04	77.31 ± 2.76	62.72 ± 1.22	82.31 ± 1.48	82.01 ± 1.31	64.76 ± 2.79	83.14 ± 1.20	82.28 ± 1.72	66.21 ± 1.78
20	92.44± 1.65	91.03± 1.59	72.32± 1.19	93.75± 2.48	92.17± 0.91	75.33± 1.52	96.56± 1.67	97.38± 2.27	77.82± 2.12
30	97.16± 2.54	96.03± 0.85	85.51± 1.86	98.67± 1.37	98.05± 1.18	87.11± 1.41	98.20± 2.62	99.50± 1.68	88.80± 1.64
45	98.48± 1.34	97.15± 1.85	93.07± 1.71	100.78± 1.61	99.18± 1.55	92.02± 1.10	98.77± 1.29	101.02 ± 1.51	94.16 ± 1.45

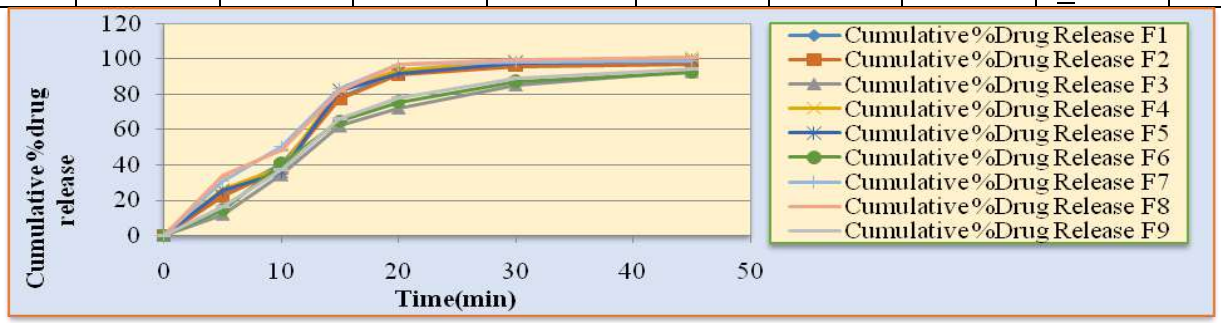

Fig. 11: Cumulative % Drug Release Vs Time

Statistical Analysis of 3^2 Factorial Designs

Fitting of Data to the Model

F1 to F9 in Design Expert 8.0.4.1 and results shown in Table 9.Best fit model was quadratic model and value of R^2, SD, and % CV are given in table12. Positive value shows positive relationship between response and factor and vice-versa.

Table 9: 3^2 Design layouts with Respective Observed Response

Factorial Batches	X_1(Drug concentration in liquid medication)	X_2(Carrier Coating Ratio)	Y_1(Cumulative % drug release at 15 min)	Y_2(Angle of Slide)(°)
F1	-1	-1	78.28	28.00
F2	0	-1	77.31	29.00
F3	1	-1	62.72	27.33
F4	-1	0	82.31	33.62
F5	0	0	82.01	32.30
F6	1	0	64.76	31.56
F7	-1	1	83.14	34.00
F8	0	1	82.28	33.66
F9	1	1	66.21	33.00

Table 10: Summary of Results of Multiple Regression Analysis for Y_1, Y_2

Dependent Variables	Y_1(Cumulative % Drug release at 15 min)		Y_2(Angle of slide)	
	Coefficients	P value	Coefficients	P value
Intercept	81.45	0.0005	32.76	0.0144
X_1	-8.34	<0.0001	0.62	0.0153
X_2	2.22	0.0045	2,72	0.0024
X_1 X_2	-0.34	.04031	-0.083	0.8270
X_1^2	-7.63	0.0006	-0.40	0.4722
X_2^2	-1.37	0.0709	-1.66	0.0427

Table 11: Summary of Quadratic Polynomial Equation for Responses Y_1, Y_2 for Fitting to Quadratic Model

Quadratic model	Quadratic polynomial equation
Y_1	$Y_1= 82.45-8.34X_1+2.22X_2-0.34X_1X_2-7.63X_1^2-1.37X_2^2$
Y_2	$Y2= 32.76-0.62X_1+2.72X_2-0.083X_1X_2-0.40X_1^2-1.66X_2^2$

The observed value for cumulative % drug release at 15 min all 9 batches F1- F9 varied from 62.72- 83.14%. The result indicates that Y_1 is affected by the independent variables selected for the study. X_1 has negative value of co-efficient, showing antagonist effect. These two variables X_1 ($P<0.05$) and X_2 ($P<0.05$) are significant in affecting Y_1. The co-efficient value for X_2 is 2.22 and is significant ($P<0.05$).Hence variable X_2 i.e. Weight ratio of carrier and coating are significant with positive effect on Y_2.

These indicate positive effect of X_1 on Y_1. The value for angle of slide (Y_2**)** of all 9 batches F1-F9 varied from 27.33. The result indicates that Y_2 is affected by the independent variables selected for the study. Out of 2 independent variables, the X_1 (0.62) and X_2 (2.72), The co-efficient value for X_2 is 2.72 and is significant ($P<0.05$). Hence variable X_2 i.e. Weight ratio of carrier and coating was found to be significant with positive effect on Y_2. These indicate positive effect of X_2 on Y_2.

Table 12: Summary of Results of Regression Analysis for Responses Y_1, Y_2 for Fitting to Quadratic Model

Quadraic Model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Y_1	0.997	0.993	0.974	0.71	0.93
Y_2	0.9734	0.9290	0.7177	0.69	2.21

Table 13: ANOVA for Dependent Variables

Source	Sum of Squares	Degrees of freedom	Mean Square	F value	P value
For Y_1 = % Cumulative drug release at 15 min					
Regression	567.56	5	113.51	228.18	0.0005
Residual	1.49	3	0.50		
Total	569.05	8			
For Y_2 = Angle of Slide					
Regression	52.64	5	10.53	21.95	0.0144
Residual	1.44	3	0.48		
Total	54.07	8			

Contour Plots and Response Surface Analysis

2D plots and 3-D plots are shown in Fig. 12, 13,14 and 15 are useful to study the interaction effects of the factors on the responses.

Effect of X_1 and X_2 on response $Y_1$and Effect of X_1 and X_2 on response Y_2

2D and 3D plots are shown in Fig. 12 and 13 which shows as carrier-coating ratio (R) (X_2) increase, increase the cumulative % drug release at 15 min and also the Erlotinib concentration in liquid medication (C_d) (X_1) increases. The drug level at 15 min decreases may be due to precipitation of drug in less amount of liquid.

Effect of X1 and X2 on response Y2

2D and 3D plots are shown in Fig. 14 and 15 which showed that angle of slide Y_2 increased on increasing the carrier-coating ratio (R) (X_2) and drug concentration in liquid medication (X_1) increase the angle of slide (Y_2) decrease.

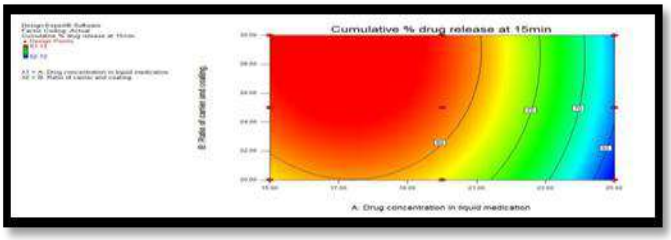

Fig. 12: 2D surface plot Effect of X_1 & X_2 on Y_1

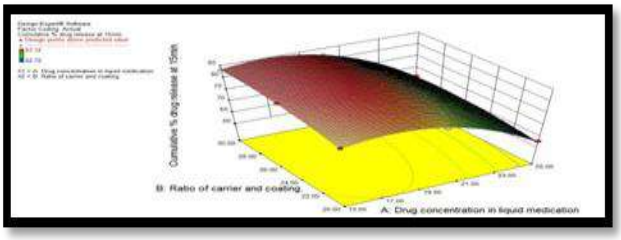

Fig.13: 3D surface plots of X_1 & X_2 on Y_1

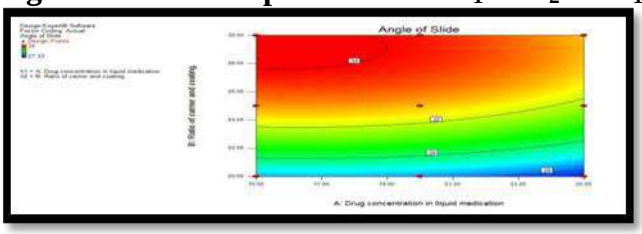

Fig. 14: 2D counter plots of X_1 and X_2 on Y_2

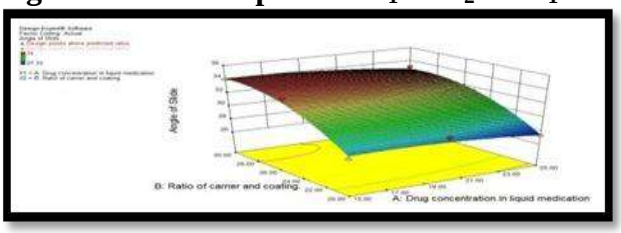

Fig.15: 3D surface plots of X_1 and X_2 on Y_2

Optimization and Validation

The check point batches & optimized batch was found from the design expert 8.0.4.1. It was randomly fix the select final batch of tablet based upon criteria 80-85% for cumulative % drug release at 15 min and 30-33° for Angle of Slide. Check point batches (O1) and (O2) were prepared as per Fig. 16 and 17. In which yellow region is the optimize region.

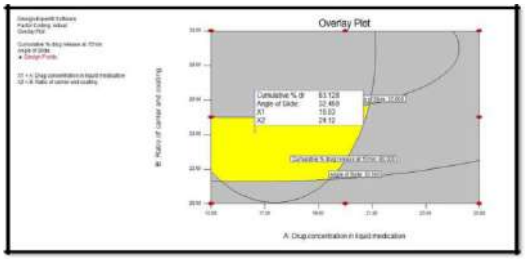

Fig.16 : Overlay Plot for O1

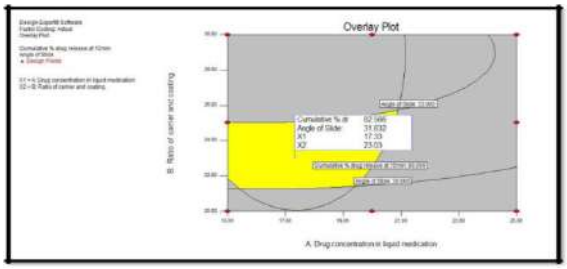

Fig.17: Overlay Plot for O_2

Table 14: Formula for Checkpoint Batches

Ingredient	Quantity (mg)	
	O_1	O_2
Erlotinib (W) (Liqiud formulation)	150.33	141.80
Carrier (Avicel PH 200)	280.91	261.85
Coating (Aerosil 200)	11.64	11.36
SSG	22.14	20.75

Table 15: in Vitro drug Release Study of O_1& O_2

Time (min)	Cumulative % drug release	
	O_1	O_2
5	23.20± 0.24	24.80 ± 0.48
10	44.02± 2.26	51.45± 1.28
15	84.66± 1.40	83.39± 2.08
20	93.41± 0.90	91.18± 0.76
30	96.82± 1.18	97.12± 0.54
45	99.72± 0.58	98.11± 0.36

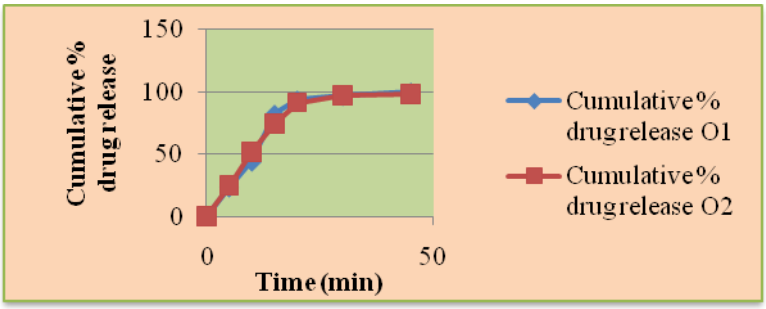

Fig.18: Drug release of batches O1 and O2

Evaluation of Checkpoint Batches

***In vitro* drug release study of check point formulations**

In vitro drug release study of O1 and O2 was shown in Table 15. O1 and O2showed drug release > 90 % at 20 minutes.

Post compression parameter of check point formulations

As shown in Table 16, the weight of O1 and O2 was found to be 466.02 ± 1.20 and 436.76 ± 1.88. Also batches passes the weight uniformity test as per as per IP (2007) specification i.e. below 5 % and friability was below 1% which indicates good mechanical strength.

Table 16: Post Compression Parameter of Optimize Formulation

Evaluation Parameter	O_1	O_2
Weight (mg)	466.02 ± 1.20	436.76 ± 1.88
Friability test (%)	Pass	Pass
Hardness (kg/cm^2)	4.44 ± 0.57	4.33 ± 0.57

Table 17: Results of Check Point Batches for Response Variables

Response Variables	O_1		O_2	
	Theoretical value	Practical value	Theoretical value	Practical value
Y_1	83.12	84.66 ± 1.40	82.56	83.39± 2.08
Y_2	32.46	31.33± 0.57	31.63	32.22± 1.00

Table 18: Comparison of % Drug Release of Optimized Batch with Marketed Product

Time (min)	Optimized	Marketed Product
0	0	0
5	23.20 ± 0.24	12.33 ± 0.57
10	44.02 ± 2.26	19.72 ± 1.26
15	84.66 ± 1.40	34.37 ± 2.21
20	93.41 ± 0.90	46.36 ± 0.78
30	96.82 ± 1.18	55.34 ± 1.68
45	99.72 ± 0.58	69.72 ± 0.64

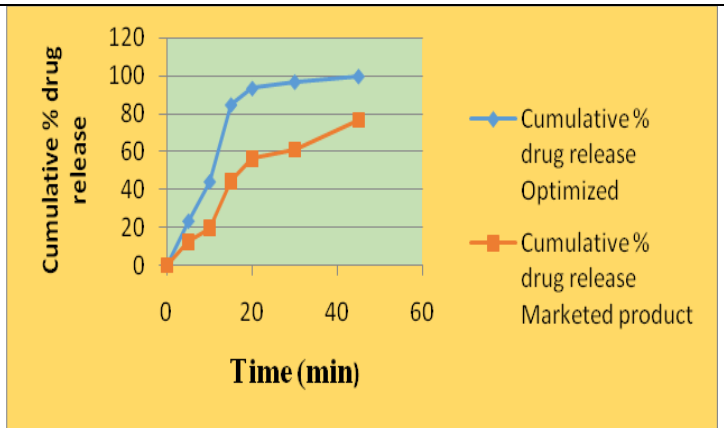

Fig 19: Comparison of Optimized Batch with Marketed Product

Results of Check Point Batches for Response Variables

From the above observations, dependent parameter i.e. angle of slide and Cumulative% drug release at 15 min was compared with predicted values. The results obtained with check point batch are close to predicted values (Table 17).

Thus, we can conclude that the statistical model is mathematically valid**.**

Formulation O1 was selected as optimized batch because of higher dissolution at 15 minute & lower angle of slide.

Comparison of % drug release of tablet of Optimized batch with marketed product

As shown in Table 18 tablet of optimized batch showed drug release > 80% in 15min while marketed product showed around 35% drug release at 15 min.

Differential Scanning Calorimetry (DSC) Analysis

Fig.20 and Fig.21 shows the thermal behavior of the pure component and thermal behavior of the optimized liquisolid compact. Pure Erlotinib shows characteristic sharp peak at around 238°C. Sharp peak is indication pure drugs crystalline nature. Now, DSC study of liquisolid system showed no peak around 238°C which indicate the drug is changed into amorphous form.

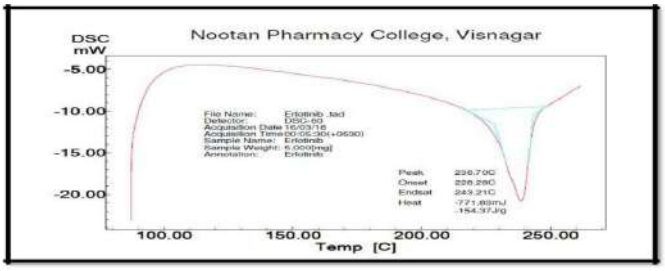

Fig. 20: DSC of Pure Drug Erlotinib

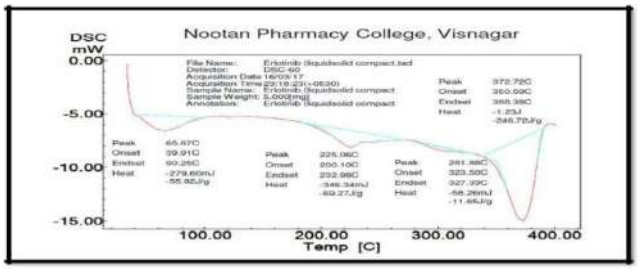

Fig21: DSC of Optimized Liquisolid Compact

Powder X-Ray Diffraction Analysis

Fig. 22 and 23 shows XRPD of Erlotinib and optimized liquisolid compact. In Fig. 22 shows sharp peak at 2θ diffraction angles which indicate its crystalline state. In Fig. 23 this sharp peak is absence which indicate Erlotinib convert to amorphous form.

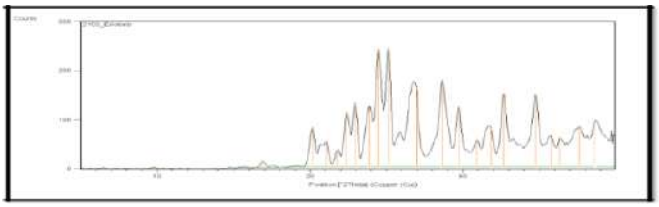

Fig. 22: XRD of Pure Drug

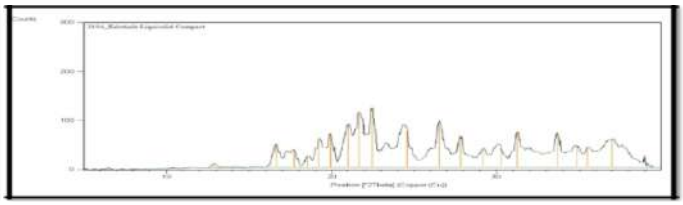

Fig. 23: XRD of Optimized Liquisolid Compact

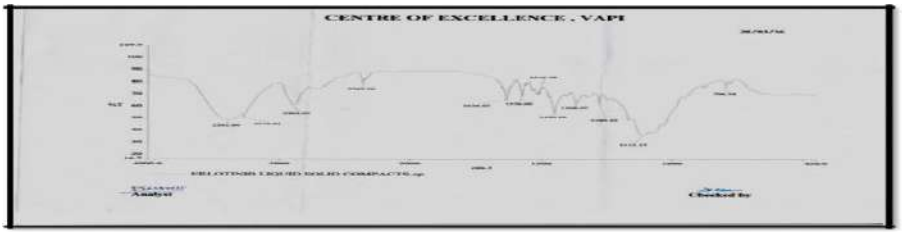

Fig. 24: FTIR spectra of Final Formulation after Stability Study

Accelerated Stability Study

FTIR spectrums of formulation after 30 days are shown in Fig. 24. All the major peaks of drug are present, indicating there is no extensive degradation of drug & drug is present in formulation.

Physicochemical Evaluations

After accelerated study no change in physical parameters as shows in Table.19.

Table 19: Stability Data of Optimized Batch

Initial		After 15 days	After 30 days
Condition:- 40 ± 2°C /75 ± 5% RH			
% Drug content:-100.23 ± 1.98		**%Drug content:**-99.46+1.08	**% Drug content:**-99.43 +1.67
Time(min)	**% CDR**		
0	0	0	0
5	23.10 ± 0.24	22.36 ± 0.72	23.19 ± 1.46
10	42.22 ± 2.26	44.26 ± 1.98	43.14 ± 1.14
15	82.02 ± 1.40	81.24 ± 0.68	81.30 ± 1.85
20	93.14 ± 0.90	92.58 ± 2.16	92.66 ± 0.96
30	97.68 ± 1.18	97.36 ± 1.78	96.68 ± 1.28
45	99.76 ± 0.58	99.48 ± 0.46	99.16 ± 0.74

Conclusion

On the basis of study, liquisolid compact of Erlotinib tablet were successfully formulated. No incompatibility between drug and excipients proof by FTIR study. Further optimization was done using Response surface methodology using independent variables like (Erlotinib concentration in liquid medication (X_1) &carrier coating ratio (X_2)) on dependent variables like (Cumulative % drug release at 15 min(Y_1) and Angle of slide (Y_2)). During study we observe carrier coating ratio increases, flow properties decrease, %drug release at 15min increase. Erlotinib concentration in liquid medication increases, Flow property increases and % drug release at 15 min decreases. On basis of the results of angle of slide and drug release profile O1 batch was selected. The angle of slide, % drug content and % CDR were found to be 32.30°, 100.23 %, 99.18 % respectively. DSC and PXRD results revealed enhancement of solubility of Erlotinib. This selected batch were go for accelerated stability study at 40ºC ± 2ºC / 75 ± 5 % RH in which shows no major change in any parameter of formulation.

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Conflict of interest

The authors declare no conflicts of interest.

References

1. Thakkar, H., Patel, B. and Thakkar, S. (2010). A Rewiew on techniques for oral bioavailability enhancement of drugs. *International Journal of Pharmaceutical review and research*, 4(3), 03-222.

2. Brahmankar, D.M., Jaiswal, S.B. (2003). Biopharmaceutics and Pharmacokinetics a treatise. Reprint of 1st ed. Vallabh Prakashan 335– 371.

3. Varandal, A.B., Magar, D.D., Saudagar, R.B, (2013). Different approaches toward the enhancement of Drug Solubility. *Journal of Advanced Pharmacy Education & Research*, 3, 415-426.

4. Nagabandi, V., Ramaraoz, T., Jayaveera, K.N. (2011). LIQUISOLID Compacts: A Novel Approach to Enhance Bioavailability of Poorly Soluble Drugs. *International Journal of Pharmacy and Biological Sciences*,1(3), 89-102.

5. Doney, Alex, B.S., Saroj, Sabitha M (2012). Mechanism of solubility of liquisolid formulation in non volatile solvent: A review. *International Journal of Pharmacy and Pharmaceutical Sciences*, 4(3),710-715.

6. Cherukuri, Sowmya, Chappidi, Reddy S, Dindigala,Vadla A, Liquisolid technique: a novel approach to enhance solubility and bioavailability of BCS-II drugs. *International Research Journal of Pharmacy*, 3(7),108-115.

7. www.drugbank.ca/drugs/db00530

8. http://pubchem.ncbi.nlm.nih.gov/compound /Erlotinib

9. Kasture, S.V., Gondkar, S.B., Darekar, A.B., Dash, P, Bhambar, K.V. (2011). Enhancement of dissolution rate of lansoprazole using liquisolid tablet technique. *International Journal of Pharmaceutical Research*, 3(2):27-31.

10. Sravana L, Srivalli P, T. Rajeev (2012): A Novel Approach for Improvement of Solubility and Bioavailability of Poorly Soluble Drugs: Liquisolid Compact Technique. International Journal of Research in Pharmaceutical and Biomedical Sciences 3:1621-1632.

11. Izhar A S, Pavani .E (2012): The Liquisolid Technique: Based Drug Delivery System.International Journal of Pharmaceutical Sciences and Drug Research 4(2):88-96.

12. Chella N, Shastri N, Tadikonda R (2012): Use of liquisolid compact technique for improvement of the dissolution rate of Valsartan.Acta Pharmaceutica Sinica B 2(5): 502-508.

13. Vaskula S, Vemula S, Bontha V, Garrepally P (2012): Liquisolid compacts: An Approach to Enhance the Dissolution rate of Nimesulide. Journal of applied Pharmaceutical Science 2(5): 115-121.

14. Ahmed S, Jabbar, Ahmed A (2013): Formulation and evaluation of Piroxicam liquisolid compacts. International journal of pharmacy and pharmaceutical sciences 5(1): 132-141.

15. Kharwade M, Sneha M A (2015): Review on Pioneering Technique - Liquisolid Compact and Applications. Research Journal of Pharmaceutical, Biological and Chemical Sciences 6(2): 220-227.

16. Sinkar NB, Gondkar SB, Saudagar RB (2015): Liquisolid systems: solubility enhancement of poor soluble drugs. World Journal of Pharmaceutical Research 4:1748-1765.

17. Fahmy RH, Kassem MA (2008): Enhancement of famotidine dissolution rate through liquisolid tablets formulation: In vitro and in vivo evaluation. European Journal of Pharmaceutics 69:993-1003.

18. Javadzadeh Y, Siahi MR, Jalali BM, Nokhodchi A (2005): Enhancement of dissolution rate of piroxicam using liquisolid compacts. International journal of pharmaceutics 60:361-365.

19. Javadzadeh Y, Navimipour B, Nokhodchi A (2007): Liquisolid technique for dissolution rate enhancement of high dose water-insoluble drug (Carbamazepine). International journal of Pharmaceutics 341:26-34.

20. Spireas S, Sadu S (1998): Enhancement of prednisolone dissolution properties using liquisolid compacts. International Journal of Pharmaceutics 166:177–188.

21. Vaskula S, Vemula S , Bontha V, Garrepally P (2012): Liquisolid Compacts: An Approach to Enhance the Dissolution Rate of Nimesulide. Journal of Applied Pharmaceutical Science 02(05):115-121 .

22. Kumpati R, Srujan M, Subrahmanyam K.V (2013): Enhancement of solubility of Nifidepine by Liquisolid compact Technique. International Journal of Innovative pharmaceutical science and research 1(2):296-309.

23. Javadzadeh Y, Musaalrezaei L, Nokhodchi A (2008): Liquisolid Technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. International Journal Of pharmaceutical 362:102-108.

24. Khaled A, Yousif A, Yousry M (2001): In vivo evaluation of Hydrochlorthiazide liquisolid tablets in beagle dogs. International journal of pharmaceutics 222:1-6.

25. Nokhodchi A, Javadzadeh Y, Shadbad M (2005): The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts.J Pharm Pharmaceut Sci 8(1):18-25.

26. Hassan MA, El-Saghir H.M (2011): Enhancement of dissolution and the anti-inflammatory effect of nimesulide, using liquisolid compact for oral application. Bull Pharm Sci 34:1-8.

27. El-Say KM, Samy AM, Fetouh MI (2010): Formulation and evaluation of rofecoxib liquisolid tablets. International Journal of Pharmaceutical Sciences Review and Research 3:132-142.

28. Sayyad FJ, Tulsankar SL, Kolap UB (2013): Design and development of liquisolid compact of Candesartan cilexetil to enhance

dissolution. Journal of pharmacyResearch 7:381-388.

29. Sandhya P, Khanam S, Bhatnagar D, Rao KSK and Subrahmanyam C.V.S (2013): Formulation and Evaluation of Liquisolid Compacts of Carvedilol. Journal of Pharmacy and Biological Science 6:26-36.

30. Bary AA, Louis D ,Sayed S (2014): Liquisolid Tablet Formulation as a Tool to Improve the Dissolution of Olmesartan Medoxomi. Inventi Journals 1:1 -8.

31. Tiong N, Elkordy AA (2009): Effects of Liquisolid formulation on Dissolution of naproxen. European Journal of Pharmaceutical and Biopharmaceutics 73;373-384.

32. Peddi MG. Novel Drug Delivery System: Liquid Solid Compacts (2013): Molecular Pharmaceutics & Organic Process Research 1:1-5.

33. Patel T, Patel LD, Suhagia BN, Soni T,Patel T (2014): Formulation of Fenofibrate Liquisolid Tablets Using Central Composite Design. Bentham Science Publishers 11:11-23.

34. Bin J, XiaotaoX, Baoyu L, MaopingP, Gingxia L (2014): Tablets containing erlotinib hydrochloride and preparation method thereof. China Patents CN 103705477 A.

35. Reguart N, Cardona AF, Rosell R (2010): Role of erlotinib in first-line and maintenance treatment of advanced non-small-cell lung cancer. Dove press journal 2:143-156.

36. wei L, Zhou F, Zhou C (2014): Role of erlotinib in the targeted treatment of non-small-cell lung cancer in Chinese patients. Dove press journal 7:253-261.

37. Bezjak A, Dongsheng T, Seymour L, Clark G, Trajkovic A, Zukin M,et al. (2006): Symptom Improvement in Lung Cancer Patients Treated With Erlotinib: Quality of Life Analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.2. Journal of clinical oncology 24:3831-3837.

38. Ganjoo KN, Wakelee H (2007): Review of erlotinib in the treatment of advanced non-small cell lung cancer. Dove medical press journal 1(4):335-346.

39. Melosky BMD, Agulnik JMD, Assi HMD (2008): Retrospective practice review of treatment of metastatic non-small-cell lung cancer with second-line erlotinib. Current oncology journal 15:271-285.

40. Williamson KA (2010): A Pharmacoeconomic Review of its Use in Advanced Non-Small Cell Lung Cancer. Adis Data Information BV 28(1):76-89.

41. Jawhari D, Alswisi M, Ghannam M, Halman J (2014): Bioequivalence of a new generic formulation of erlotinib hydrochloride 150 mg tablets versus tarceva in healthy volunteers under fasting condition. An open access journal 6(4):119-123.

42. Wang Y, Schmid BG, Zhou C (2011): Erlotinib in the treatment of advanced non-small cell lung cancer: an update for clinicians. Therapeutic Advances in Medical Oncology 4(1):19-29.

43. Spireas, Spiridon, Bolton, Sanford M (1999): Liquisolid systems and methods of preparing same. US Patents, US 5968550 A.

44. Huang L, Gao S (2009): Amorphous form of Erlotinib hydrochloride and its solid amorphous Dispersion. US Patents, US 7625911 B2.

45. Hiroyuki H, Ichairou H, Akira Y (2007): Method for coating solid dispersion with film. European Patent Office KR20070103709 (A).

46. Bolton S, Spireas S (2002): Liquisolid system and method of preparing same. World Intellectual Property Organization IL127295.

47. Bolton S. and Spireas (2011): Liquisolid system and method of preparing same. European Patent Office HK1022844 (A1).