Section: Research Paper

DESIGN DEVELOPMENT AND CHARACTERIZATION OF ERLOTINIB NANOPARTICLES

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Abstract

Cancer is a disease that can affect any region of the body. Cancer from other organs may also spread to the lungs. Epidermal growth factor receptor (EGFR) is majorly responsible for the growth and development of pancreatic and lung cancer. Erlotinib belongs to the reversible tyrosine kinase inhibitor class of drugs which is give to cure non small cell lung cancer and advanced pancreatic cancer. It acts mainly upon the epidermal growth factor receptor (EGFR) which belongs to ErbB receptor family. Polymeric PLGA nanoparticles were prepared employing a modified single emulsification (o/w) comprising solvent evaporation method. In the modified method, Erlotinib (150 mg) and PLGA at different concentrations i.e., 50, 75 and 100mg; both were solubilized in Dimethyl Sulfoxide (4 ml) to make an organic phase in one beaker vessel. In some other glass beaker, an aqueous phase was made by adding Tween 80 using different concentrations like 70, 95 and 120 mg. An o/w emulsion was constituted further by mixing both the aqueous and organic phase together using probe sonicator at different time 3, 5.5, 8 min. The optimized nanoparticles were obtained with particle size range which can be effective in prolonging the circulation time of the drug helping in the delivery of the drug at the target site. The mathematical developed models can be used further for the formulation of nanoparticles with the desired characteristics.

Keywords: Cancer, Erlotinib, sonicator, PLGA, Nanoparticles etc.

Introduction

Cancer is a disease that can affect any region of the body [1]. Epidermal growth factor receptor (EGFR) is majorly responsible for the growth and development of pancreatic and lung cancer. Erlotinib belongs to the reversible tyrosine kinase inhibitor class of drugs which is give to cure non small cell lung cancer and advanced pancreatic cancer. It acts mainly upon the epidermal growth factor receptor (EGFR) which belongs to ErbB receptor family. Particulate dispersions or solid particles with a size between 10 and 1000 nm are referred to as nanoparticles [2]. The goal of drug entrapment in nanoparticles is either improved delivery or absorption by target cells or a decrease in the toxicity of the free drug to organs other than the target cells. PLGA is a biodegradable copolymer ester of two α-hydroxy acids (lactic and glycolic acids) and PLGA nanoparticles are efficiently taken up by M cells across the intestinal epithelial cell, thus promoting a strong immune response.

Materials and Methods

Materials

Erlotinib was obtained as a gift sample from Sun Pharmaceutical, Gurgaon, India. PLGA, Methanol was obtained from Merck, India Ltd., India. Tween 80 was obtained from Loba Chemie Pvt. Ltd. Mumbai, India. Sodium chloride, sodium bicarbonate, calcium chloride dihydrate, potassium chloride, sodium hydroxide and polyvinyl alcohol and other ingredients were taken from the labs of Baba Mastnath University, Rohtak, All chemicals were of HPLC grade and used as given by the manufacturer.

Methods

Estimation of λ_{max}

A sample 10 µg/ml was scanned between 200-400 nm to obtain the λ_{max} for Erlotinib [3].

Preparation of Calibration Curve of Erlotinib in Methanol

Dilutions were taken from the stock solution in the concentration range of 1-6 µg/ml and by using UV spectrophotometer the absorbance of each sample was measured at λ_{max}. Taking these readings on calibration curve was plotted by taking concentration of Erlotinib in X-axis and corresponding absorbance in Y axis [3].

Drug- Excipient Compatibility Study

FTIR Technique [4]

The drug excipient interaction study was carried out to check whether there is an interaction occurs in between drug and polymer. The FTIR obtained from drug and polymers combination must be compared with the pure drug spectra. Fourier transform IR spectra were recorded on FTIR Alpha, Bruker, Germany.

DSC Analysis [5]

DSC measurements were carried out on DSC Q10 (Waters Corporation, USA). The instrument was calibrated using Indium as standard. Samples were placed in sealed aluminium pans and heated from 30 ºC to 300 ºC at a rate of 10 ºC/min under nitrogen atmosphere (60 ml/min), with empty pan as reference.

Development and Optimization of Nanoparticles

Polymeric PLGA nanoparticles were prepared employing a modified single emulsification (o/w) comprising solvent evaporation method. In the modified method, Erlotinib (150 mg) and PLGA at different concentrations i.e., 50, 75 and 100 mg; both were solubilized in Dimethyl Sulfoxide (4 ml) to make an organic phase in one beaker vessel. In some other glass beaker, an aqueous phase was made by adding Tween 80 using different concentrations like 70, 95 and 120 mg. An o/w emulsion was constituted further by mixing both the aqueous and organic phase together using probe sonicator at different time 3, 5.5, 8 min. The obtained emulsion was stirred continuously for about 4 hours using magnetic stirrer at 500 rpm to ensure evaporation of organic solvent and the residual nanoparticles were left and washed thrice applying centrifugation force at 15000 rpm. The washed pellets were redissolved in 5% mannitol solution for cryoprotection. Subsequently, dried nanoparticles were obtained following lyophilization for 24 hours.

Formulation Development Using Box-Behnken Design

A category of second-order designs known as Box-Behnken designs is based on incomplete factorial designs with three levels. There are three components to this design. The polynomial equation obtained by Box–Behnken design software is as follows:

$$\mathbf{Yi = b0 + b1X1 + b2X2 + b3X3 + b12X1X2 + b13X1X3 + b23X2X3 + b11X^2_1 + b22X^2_2 + b33X^2_3}$$

Where Yi is the dependent variable, b0 is the intercept, b1 to b33 are the regression coefficients, and X1, X2, and X3 were the independent variables that were selected from the preliminary experiments. In the present study, polymer concentration, Concentration of Surfactant, and Sonication time were chosen as critical factors. The independent and dependent variables are listed in Table 1.

Table 1: Independent Variables and Their Levels in Box–Behnken Design

Variable	**Level**		
Independent variables	**Low (+1)**	**Medium (0)**	**High (-1)**
X1: Concentration of Polymer (mg)	50	75	100
X2: Concentration of Surfactant (mg)	70	95	120
X3: Sonication Time (min)	3	5.5	8
Coded values			
Dependent variables			
Y1 = particle size (nm)			
Y2 = Entrapment efficiency (EE)			

Table 2: Formulation obtained by Box–Behnken Design

Formulation Code	**Conc. of PLGA (mg)**	**Conc. of Surfactant (mg)**	**Sonication Time (min)**
F_1	100	95	8
F_2	75	70	8
F_3	50	70	5.5
F_4	100	70	5.5
F_5	75	95	5.5
F_6	100	120	5.5
F_7	75	120	8
F_8	75	70	3
F_9	50	120	5.5
F_{10}	75	120	3
F_{11}	100	95	3

F_{12}	75	95	5.5
F_{13}	50	95	3
F_{14}	75	95	5.5
F_{15}	50	95	8

Results and Discussion

Determination of λ_{max} of Erlotinib

The scanning of Erlotinib in methanol (10 µg/ml) revealed the λ_{max} to be 246 nm.

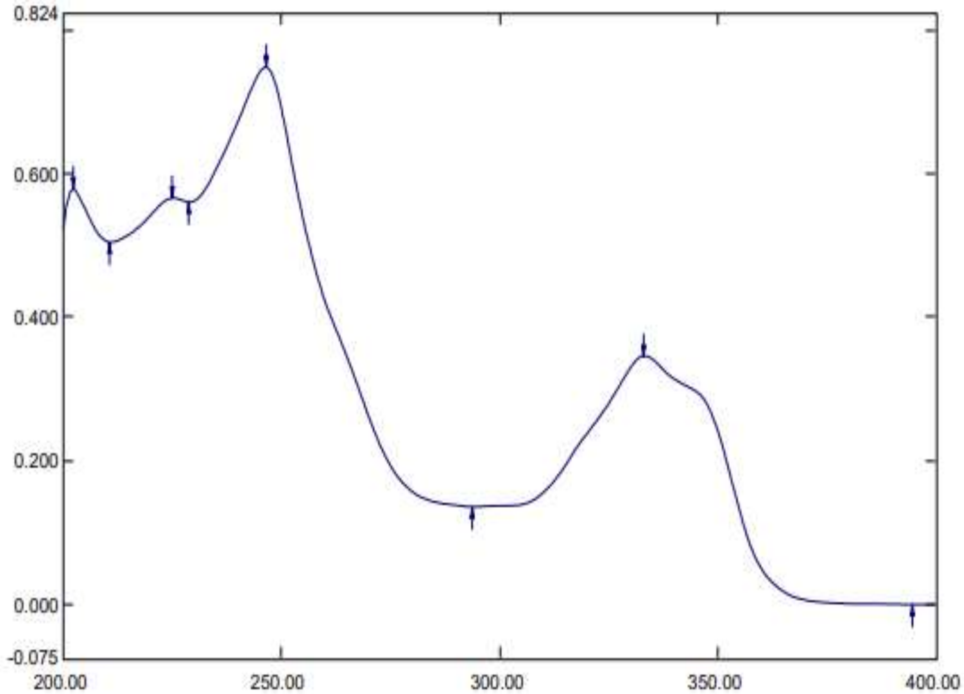

Figure 1: UV spectrum of Erlotinib in Methanol

Preparation of Calibration Curve of Erlotinib in Methanol

Standard calibration curve of Erlotinib was prepared by using methanol with the help of standard solutions of 1-6 µg/ml concentrations. The observed equation for a straight line is y= 0.151x + 0.002 with regression coefficient of 0.986. On the basis of this calibration curve calculation of drug content, in vitro diffusion release, and stability studies was done.

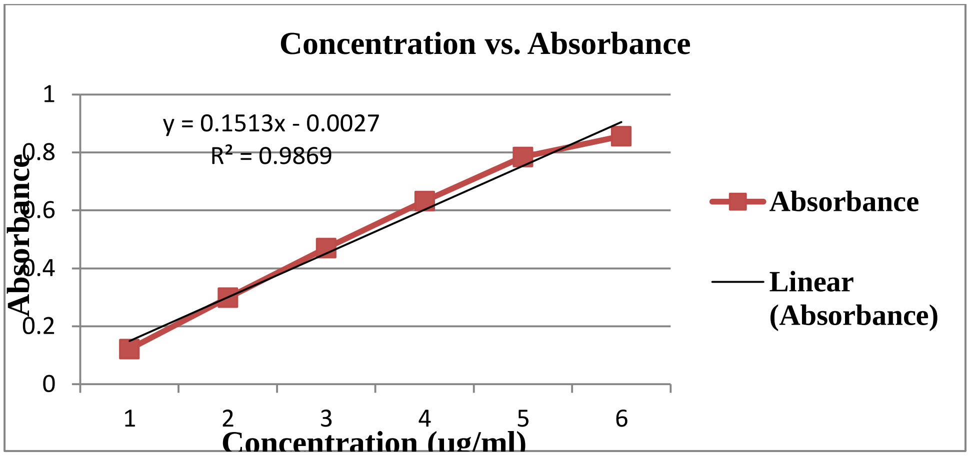

Figure 2: Calibration Curve of Erlotinib in Methanol

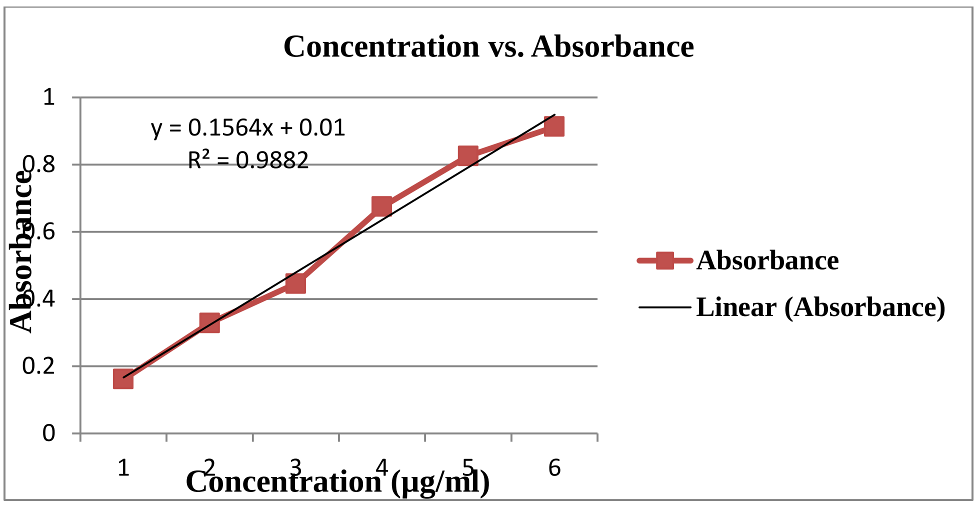

Figure 3: Calibration Curve in Phosphate Buffer (pH 6.8)

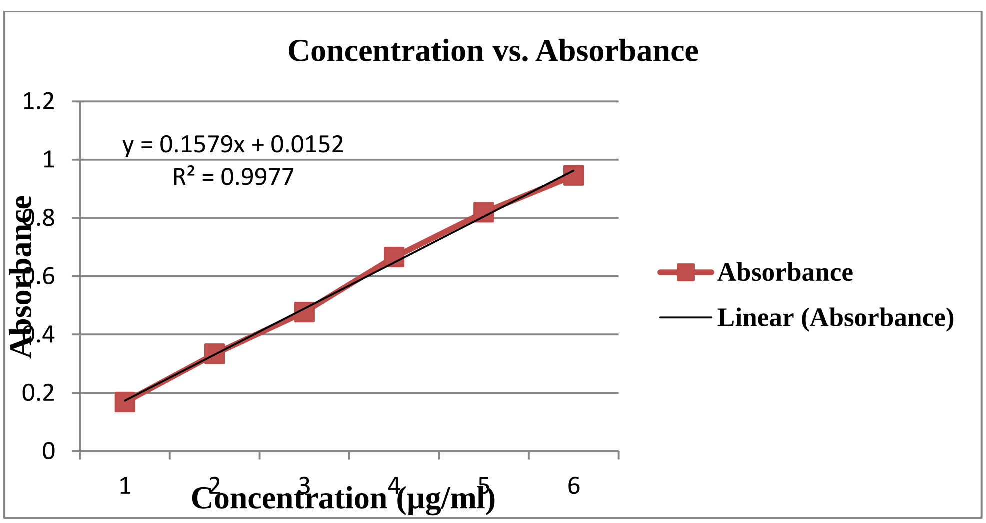

Figure 4: Calibration Curve using 0.1N HCl

The results and statistical parameters were analysed after UV spectral analysis of the drug in different media which are summarized below in Table 3.

Table 3: Result of regression analysis of UV method for estimation of Erlotinib

Statistical Parameters	**Different Media Used**		
	Methanol	**Phosphate Buffer (pH 6.8)**	**0.1N HCl**
Regression equation (Y = mx + C)	0.151x - 0.002	0.156x + 0.01	0.157x + 0.015
Slope (m)	0.151	0.156	0.157
Intercept (C)	0.002	0.01	0.015
Correlation Coefficient (r^2)	0.986	0.988	0.997

Compatibility Studies

Compatibility studies were done using FTIR and DSC. According to the FT-IR results, the characteristic bonds were observed for the pure drug powder (Erlotinib) and polymer. There was no significant difference in the FTIR spectra of Erlotinib and drug loaded nanoparticles. No significant shifting of functional peaks, no overlapping of characteristic peaks and also no appearance of new peaks were observed upon comparison of obtained spectra with reference spectra.

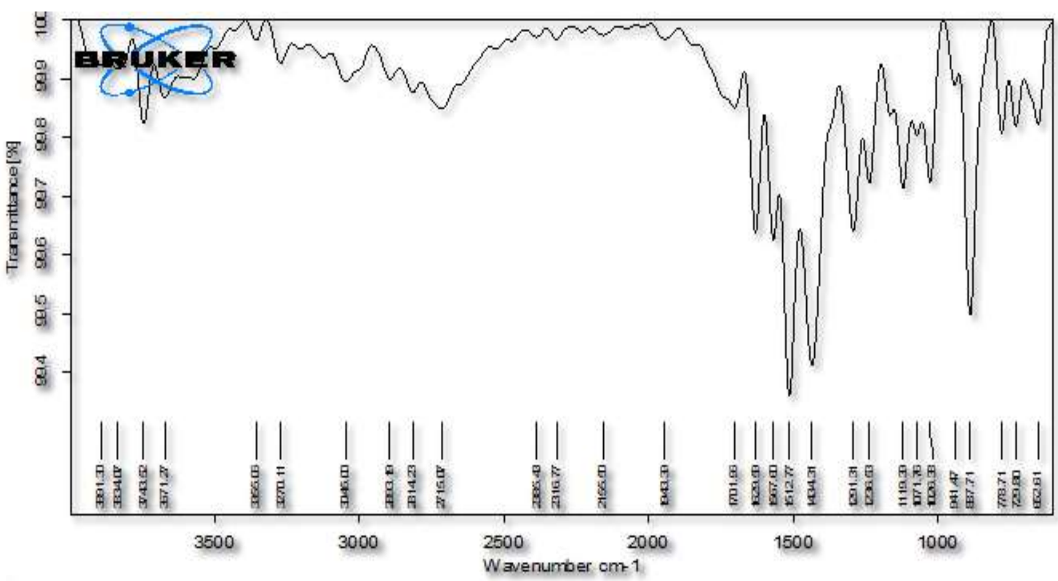

Fig 5: FTIR peak of Pure Drug

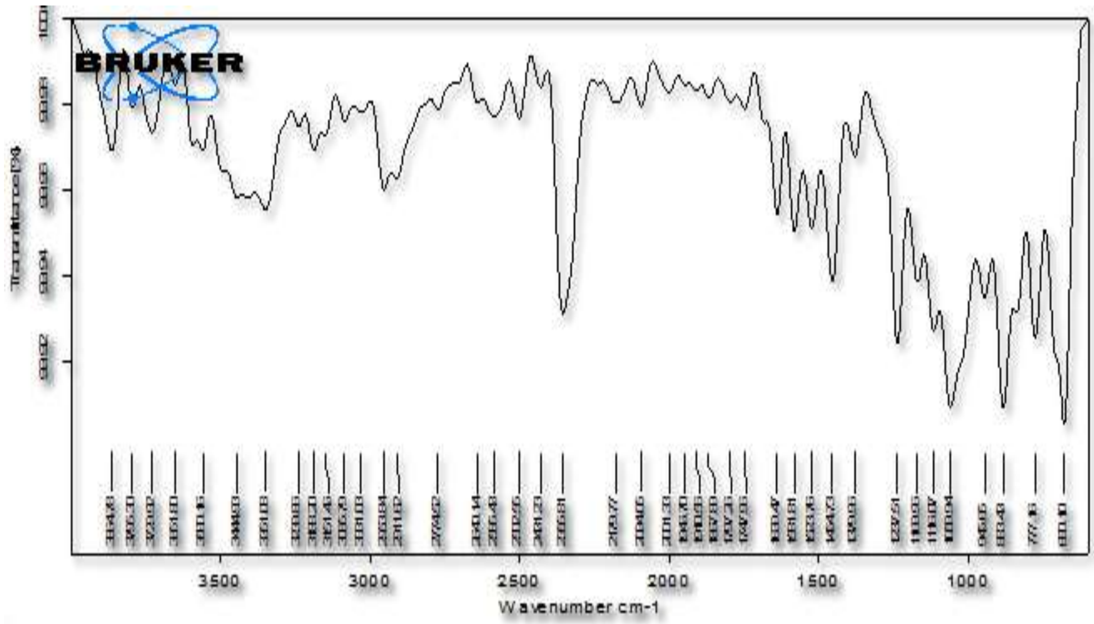

Fig 6: FTIR of Formulation

Differential Scanning Calorimetry (DSC)

The drug was confirmed by differential scanning calorimetry (DSC) analysis and there was a sharp peak at 234.87 ºC almost corresponding to its melting point (232 ºC) with percentage purity 99.11% Fig. The nano-entrapment process produced a marked decrease in crystallinity of erlotinib and allows a nearly amorphous state.

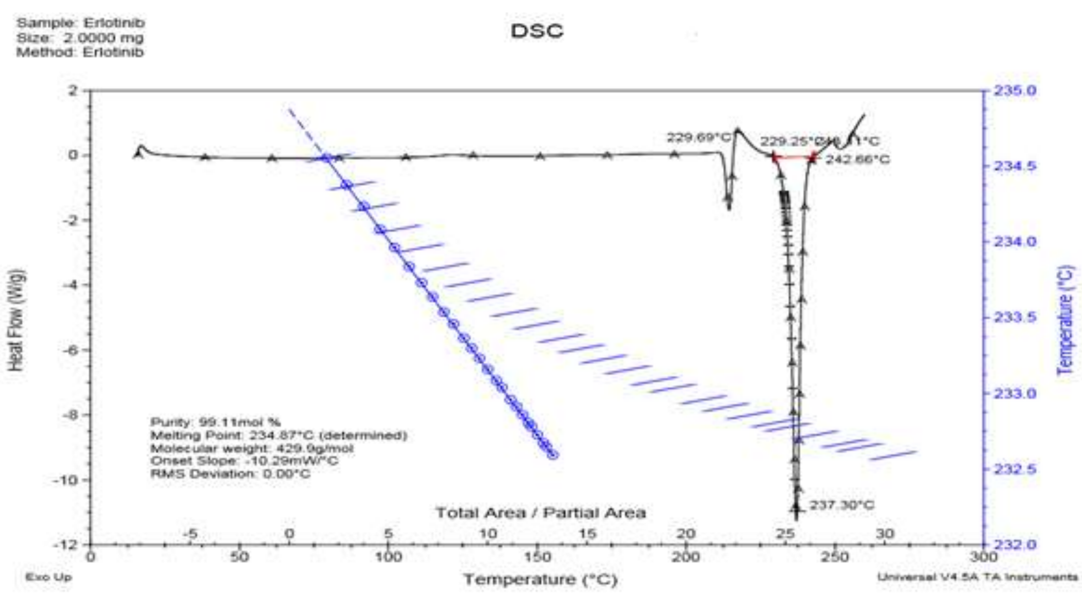

Fig 7: DSC Thermogram of Pure Drug (Erlotinib)

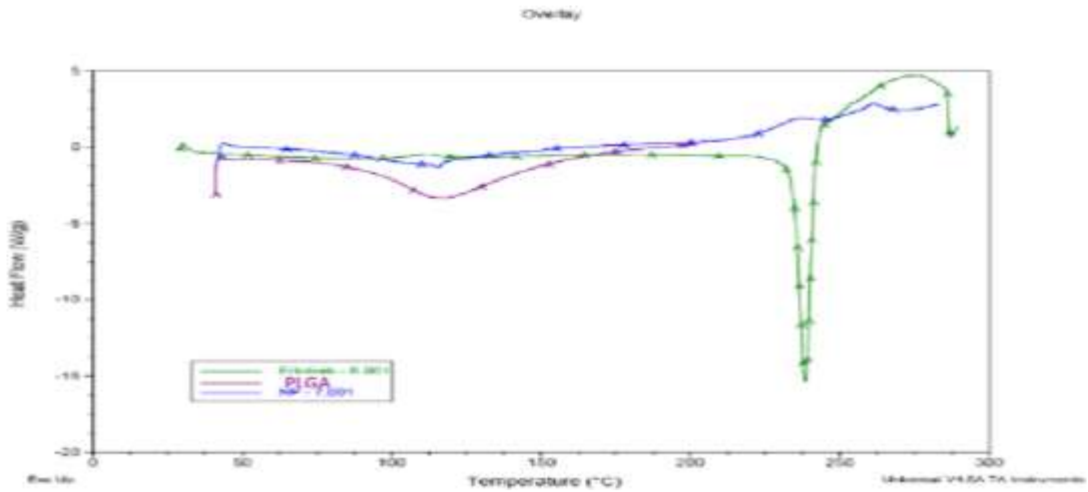

Fig 8: DSC Thermogram of Physical Mixture

The results of DSC study were in good agreement with the results of FTIR analysis.

Evaluation of Prepared Nanoparticles

Particle Size Analysis [6]

The particle size of Erlotinib nanoparticles formulation batches (F1-F15) was ranged between 108.1 -541.1 nm. Particle size can be analysed with the help of Dynamic Light Scattering method which gives information about average diameter of the particle size and distribution range of particles from 0.130 to 0.988 by Polydispersity index. The average particle size of F9 was found to be 108.1 nm and its Polydispersity index was 0.556.

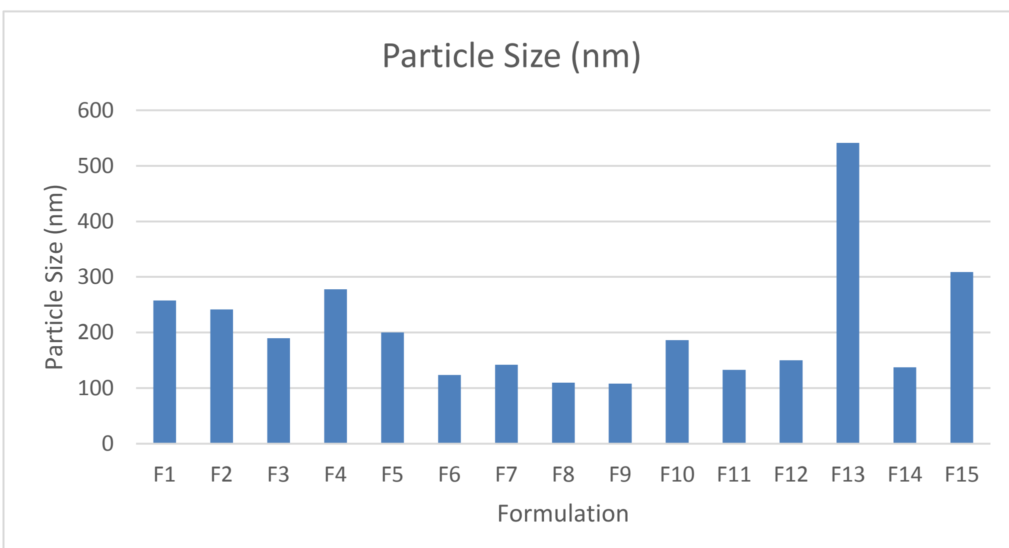

Figure 9: Bar Diagram of Particle Size

ANOVA for Quadratic Model

Table 4: Response 1: Particle Size

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	1.217E+05	9	13520.00	1.31	0.4005	not significant
A-Conc. of PLGA	15870.49	1	15870.49	1.54	0.2694	
B-Conc. of Surfactant (Tween 80)	8414.94	1	8414.94	0.8175	0.4074	
C-Sonication Time	51.31	1	51.31	0.0050	0.9465	
AB	1318.42	1	1318.42	0.1281	0.7350	
AC	31872.96	1	31872.96	3.10	0.1388	
BC	7751.04	1	7751.04	0.7530	0.4252	
A^2	19615.26	1	19615.26	1.91	0.2260	
B^2	16702.83	1	16702.83	1.62	0.2587	
C^2	17079.09	1	17079.09	1.66	0.2541	
Residual	51469.42	5	10293.88			
Lack of Fit	50009.62	3	16669.87	22.84	0.0422	significant
Pure Error	1459.81	2	729.90			
Cor Total	1.731E+05	14				

Factor coding is **Coded**.

Sum of squares is **Type III – Partial.**

The **Model F-value** of 1.31 implies the model is not significant relative to the noise. There is a 40.05% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case there are no significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The **Lack of Fit F-value** of 22.84 implies the Lack of Fit is significant. There is only a 4.22% chance that a Lack of Fit F-value this large could occur due to noise. Significant lack of fit is bad so model is required to fit it. Coefficients in coded value are represented in table. The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant.

Table 5: Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	169.07	1	58.58	18.49	319.64	
A-Conc. of PLGA	-44.54	1	35.87	-136.75	47.67	1.0000
B-Conc. of Surfactant (Tween 80)	-32.43	1	35.87	-124.64	59.78	1.0000
C-Sonication Time	-2.53	1	35.87	-94.74	89.68	1.0000
AB	-18.16	1	50.73	-148.56	112.25	1.0000
AC	89.27	1	50.73	-41.14	219.67	1.0000
BC	-44.02	1	50.73	-174.42	86.38	1.0000
A^2	72.89	1	52.80	-62.84	208.62	1.01
B^2	-67.26	1	52.80	-202.99	68.47	1.01
C^2	68.01	1	52.80	-67.72	203.74	1.01

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

The particle size of Erlotinib nanoparticles in the current study varied between 57.36-541.1 which may be regarded as a suitable midrange that contributed to reasonable homogeneity and a satisfactory size distribution. The one-way ANOVA produced the following equation.

Particle Size = 459.622 - 24.370A + 25.20B - 160.92C - 0.029AB + 1.428AC - 0.704BC + 0.11A^2 - 0.107B^2 + 10.88C^2

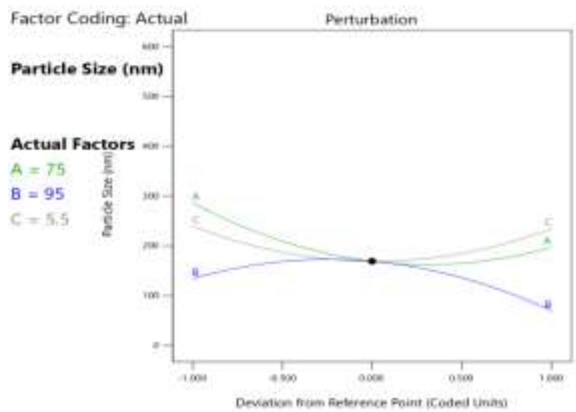

Fig 10: Main Effect; illustrating the effects of amount of Polymer, Surfactant and Sonication Time on response R1 (Particle size)

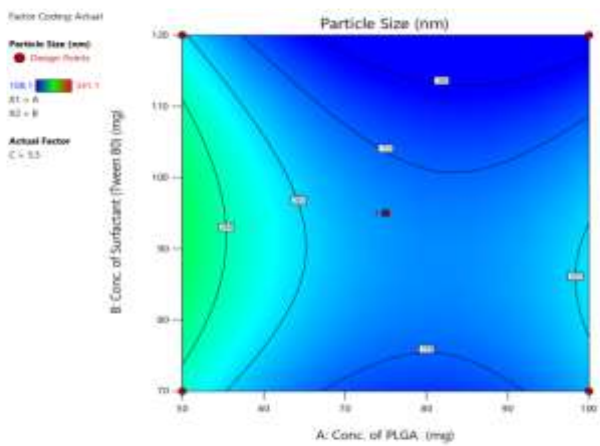

Figure 11: Contour graph showing the effect of independent factors on R1 (Particle size)

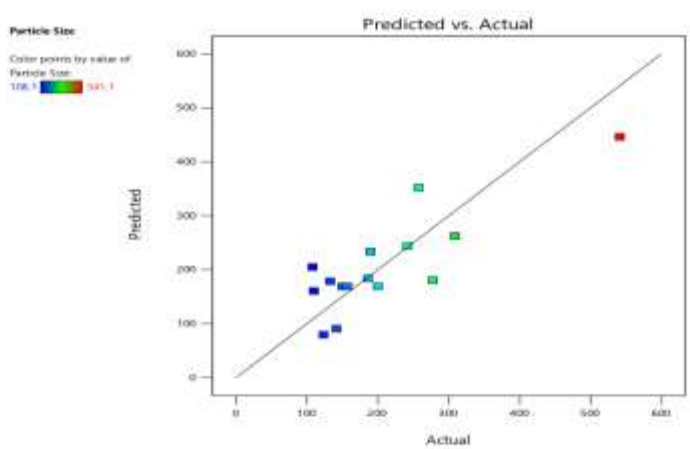

Fig 12: Graphical Representation showing Predicted vs Actual Value

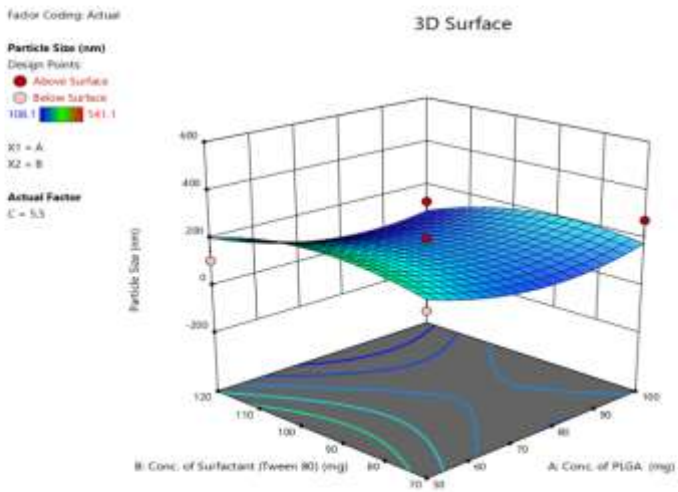

Figure 13: 3D graph showing the effect of independent factors on R1 (Particle size)

Entrapment Efficiency

Erlotinib loaded nanoparticles were characterized for entrapment efficiency. The results obtained are shown below ranging 55.36 to 74.45.

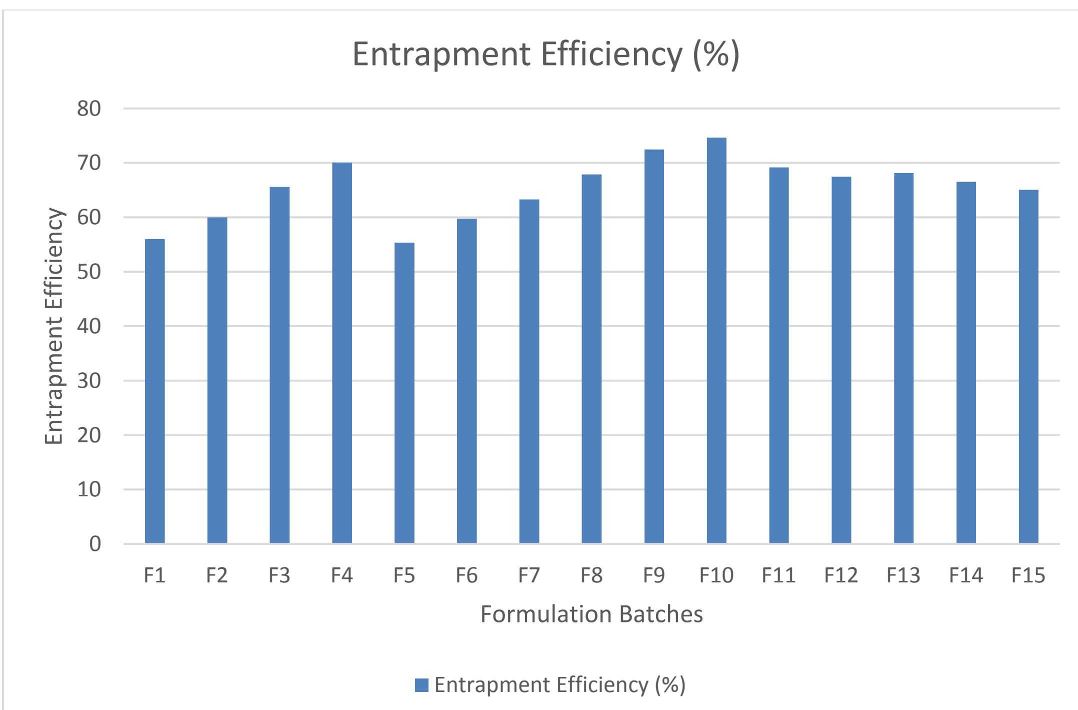

Fig 14: Entrapment Efficiency Erlotinib Nanoparticles (F1-F15)

ANOVA for Quadratic model

Response 2: Entrapment Efficiency

Table 6: ANOVA for Response 2 (Entrapment Efficiency)

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	330.01	9	36.67	1.60	0.3151	not significant
A-Conc. of PLGA	32.68	1	32.68	1.42	0.2863	
B-Conc. of Surfactant (Tween 80)	5.48	1	5.48	0.2386	0.6459	
C-Sonication Time	157.09	1	157.09	6.84	0.0473	
AB	73.79	1	73.79	3.21	0.1330	
AC	25.65	1	25.65	1.12	0.3388	
BC	2.96	1	2.96	0.1289	0.7343	
A^2	3.70	1	3.70	0.1610	0.7048	
B^2	29.95	1	29.95	1.30	0.3051	
C^2	0.8171	1	0.8171	0.0356	0.8578	
Residual	114.79	5	22.96			
Lack of Fit	23.83	3	7.94	0.1746	0.9054	not significant
Pure Error	90.96	2	45.48			
Cor Total	444.80	14				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 1.60 implies the model is not significant relative to the noise. There is a 31.51% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case C is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The **Lack of Fit F-value** of 0.17 implies the Lack of Fit is not significant relative to the pure error. There is a 90.54% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good so model is required to fit it.

Table 7: Coefficients in Terms of Coded Factors

Factor	**Coefficient Estimate**	**df**	**Standard Error**	**95% CI Low**	**95% CI High**	**VIF**
Intercept	63.13	1	2.77	56.02	70.24	
A-Conc. of PLGA	-2.02	1	1.69	-6.38	2.33	1.0000
B-Conc. of Surfactant (Tween 80)	0.8275	1	1.69	-3.53	5.18	1.0000
C-Sonication Time	-4.43	1	1.69	-8.79	-0.0766	1.0000
AB	-4.30	1	2.40	-10.45	1.86	1.0000
AC	-2.53	1	2.40	-8.69	3.63	1.0000
BC	-0.8600	1	2.40	-7.02	5.30	1.0000
A^2	1.00	1	2.49	-5.41	7.41	1.01
B^2	2.85	1	2.49	-3.56	9.26	1.01
C^2	0.4704	1	2.49	-5.94	6.88	1.01

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable. The collected ANOVA data produced the following equation:

Entrapment Efficiency = 63.13 - 2.02A + 0.8275B - 4.43C - 4.30AB - 2.53AC - 0.8600BC + 1.00A^2 + 2.85B^2 + 0.4704C^2

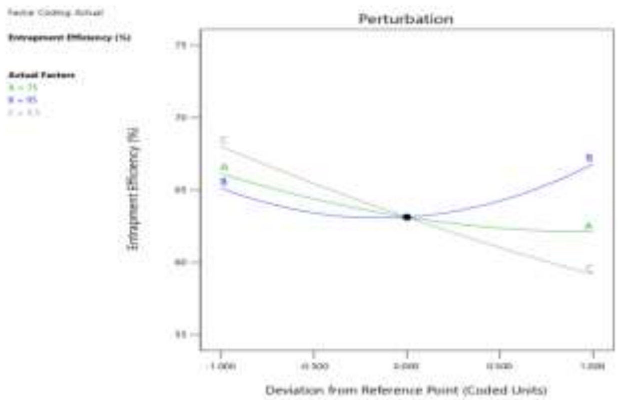

Fig 15: Main Effect; illustrating the effects of independent variable on response R2 (Entrapment Efficiency)

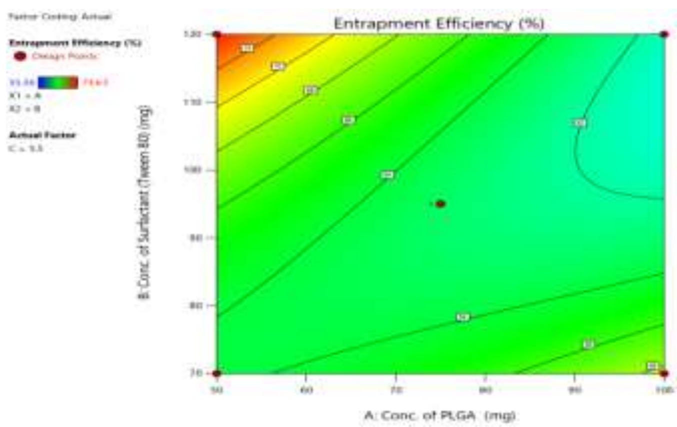

Figure 16: Contour graph showing the effect of independent factors on Y1 (Entrapment Efficiency)

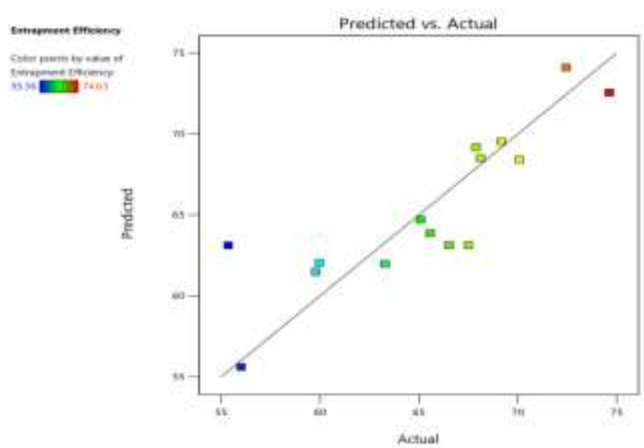

Figure 17: Graphical Representation showing Predicted vs Actual Value

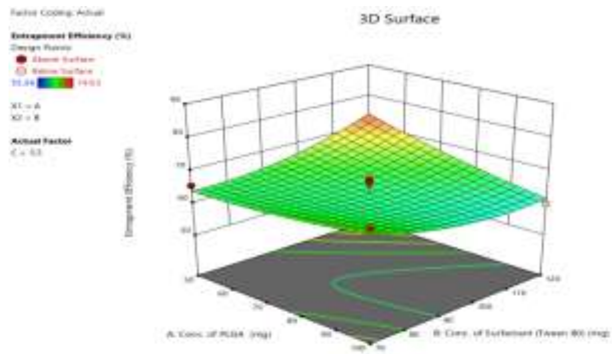

Figure 18: 3D graph showing the effect of independent factors on R1 (Entrapment Efficiency)

Checkpoint Analysis

The proposed regression models' superior prediction abilities were supported by the experimental and anticipated R^2 values. Additionally, the ratios of the actual to expected values showed low error rates, and there were acceptable residuals between the projected and experimental results; this shows that the data were not curved and that the model was adequate.

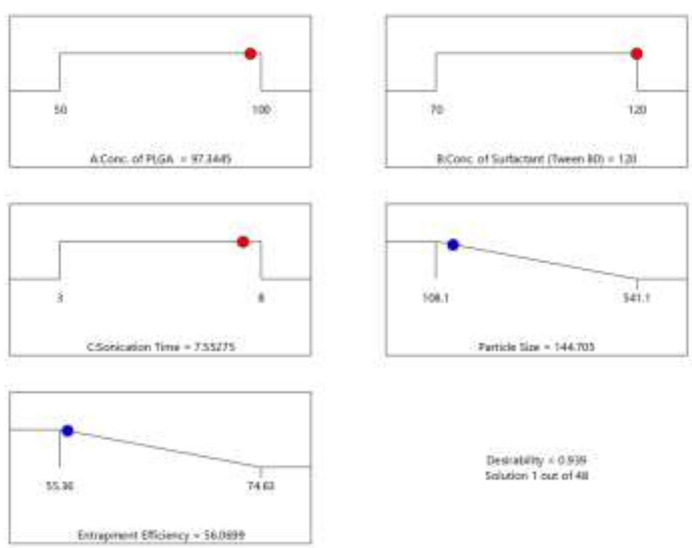

Figure 19: Ramp of desirability for the optimization process. The desired ramp depicts the levels of variables and anticipated values for the dependent variables of the optimized Erlotinib Nanoparticles Formulation

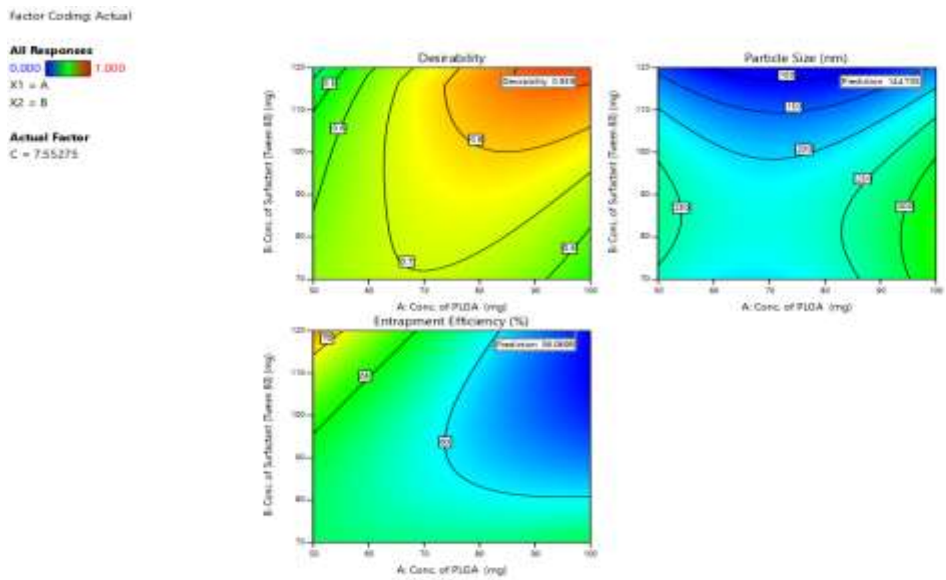

Figure 20: Contour graph of predicted responses and desirability

Drug Loading Capacity and Percentage Yield [7]

The formulated batches were evaluated for loading capacity using the formula given below.

$$\text{Loading Capacity (\%)} = \frac{\text{Total drug} - \text{Free Drug} \times 100}{\text{Nanoparticles weight}}$$

$$\text{Percentage Yield (\%)} = \frac{\text{Total Nanoparticles Weight} \times 100}{\text{Total solid Weight}}$$

The loading capacity of the formulation batches (F1-F15) were found between 55.45 ± 0.19 - 77.09 ± 0.11 and the percentage yield was found between 24.15 - 45.05.

Zeta Potential Analysis

The Malvern zeta sizer was used for analysis of the formulation prepared. Out of the fifteen batches formed, Formulation-9 (F9) was found to be -26.0 mV.

In-vitro Drug Release Studies [8]

In vitro drug release of Box Behnken designed erlotinib loaded PLGA nanoparticles using sonication technique was evaluated using 0.1N hydrochloric acid and PB pH 6.8 by dialysis bag diffusion technique. The cumulative drug release of all the batches in 0.1N hydrochloric acid ranged from 57.62±0.17 percent to 88.36±0.98 percent after 24 hrs. Out of all the formulations, F-9 containing the low value of polymer (PLGA), the high value of surfactant (Tween 80) and mid value of sonication time had shown maximum release i.e. 88.36±0.98 percent of erlotinib loaded PLGA nanoparticles in 0.1N hydrochloric acid after 24 hrs. The higher percent CDR was found in an acidic buffer in comparison to basic buffer as erlotinib is a free base and is more susceptible to dissolve in the acidic solution.

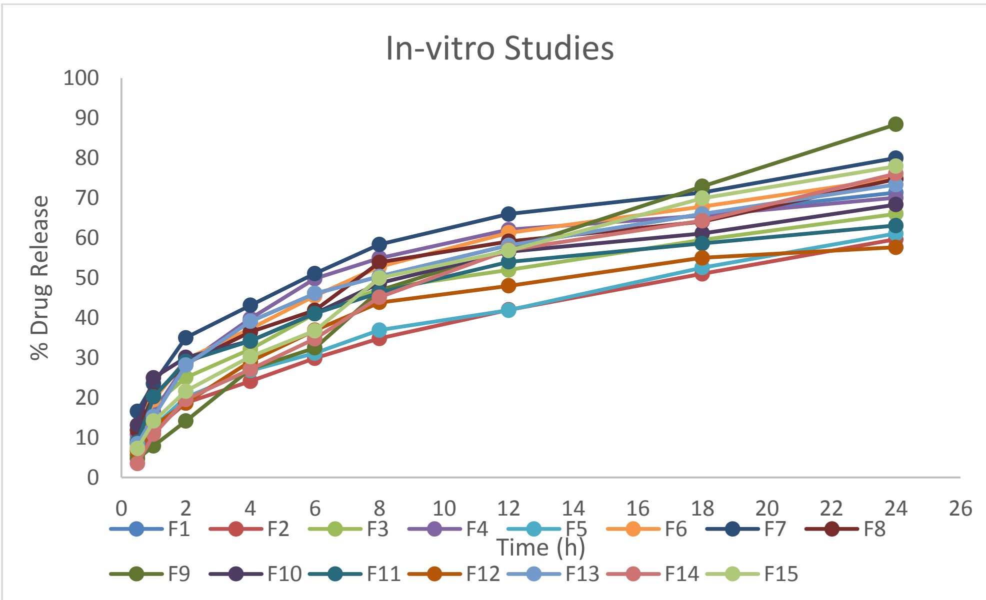

Fig 21: In-vitro drug release studies

Evaluation of Optimized Erlotinib Nanoparticles

FTIR Analysis

According to the FT-IR results, the characteristic bonds were observed for the pure drug powder (Erlotinib) and polymer. Any shift or appearance change in the characteristic bonds was not identified in the physical mixture.

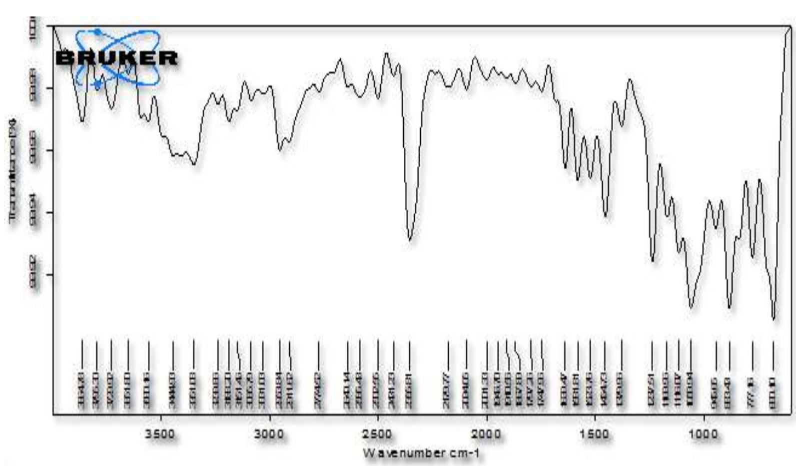

Fig 22: FTIR of Formulation 9 (optimized)

In-vitro studies of optimized formulation (F9)

In vitro drug release of the optimized formulation was evaluated using 0.1N HCl and Phosphate Buffer (pH 6.8) by dialysis bag diffusion method.

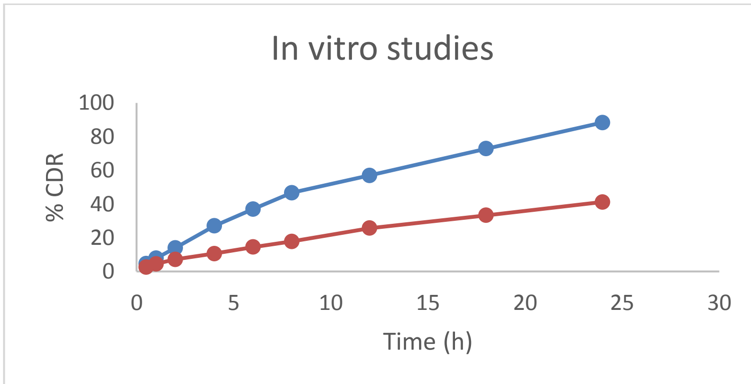

Fig 23: % CDR in 0.1N HCl and Phosphate Buffer (pH 6.8) of formulation F9

Table 8: The compiled results of the optimized batch are mentioned below in the table given below.

Code	Particle Size	PDI	EE (%)	Zeta potential	% Yield	Loading Capacity	In vitro studies	
							0.1N HCl	PBS (pH 6.8)
F9	108.1	0.556	**74.45±0.16**	-26.0	**45.05**	**77.09 ±0.11**	88.36 ±0.98	41.22 ±0.17

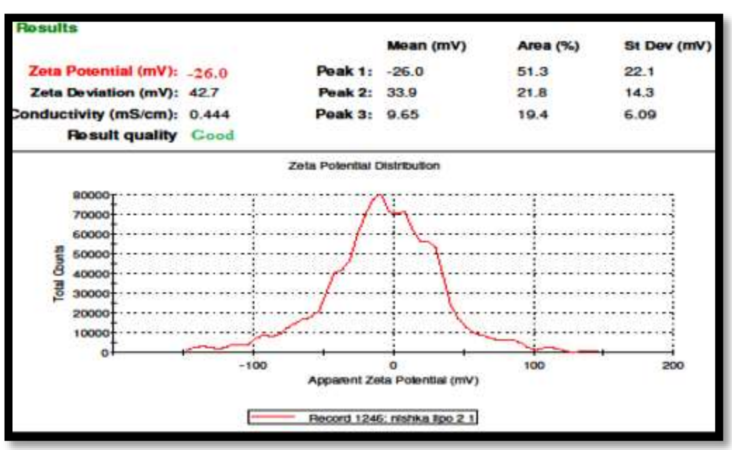

Figure 24: Zeta Potential Analysis of Optimized Formulation (F9)

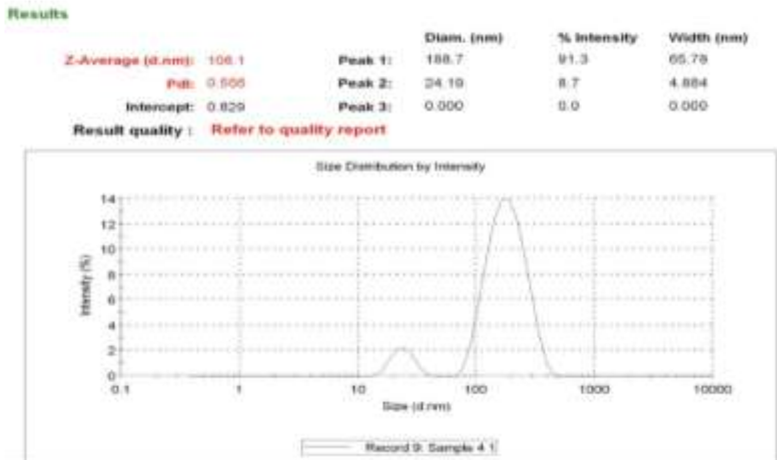

Figure 25: Particle Size Analysis of the Optimized Formulation (F9)

SEM Analysis

The prepared nanoparticles were checked for their shape and surface morphology with the help of scanning electron microscopy (Scanning Electron Microscope (SEM) - Zeiss EVO40) which indicated the spherical shaped particles with rough surface. The studies done showed the spherical shape with smooth surface nanoparticles as shown in figure.

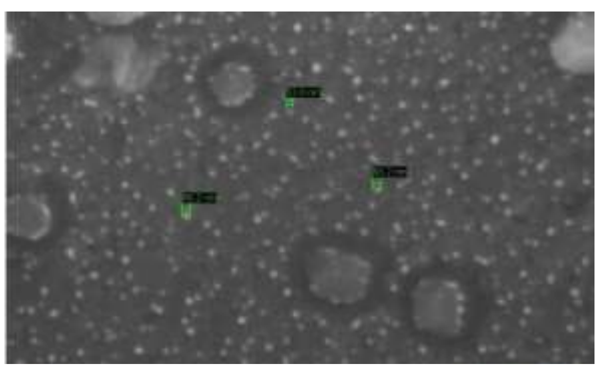

Figure 26: SEM images of Erlotinib Nanoparticles

TEM Analysis

The shape and surface morphology of the optimized Erlotinib formulation (F9) were observed by TEM. The image revealed spherical and uniform shape with a smooth surface. There was no aggregation and this was confirmed by the high zeta potential value which reflecting the stability and dispersibility of the system.

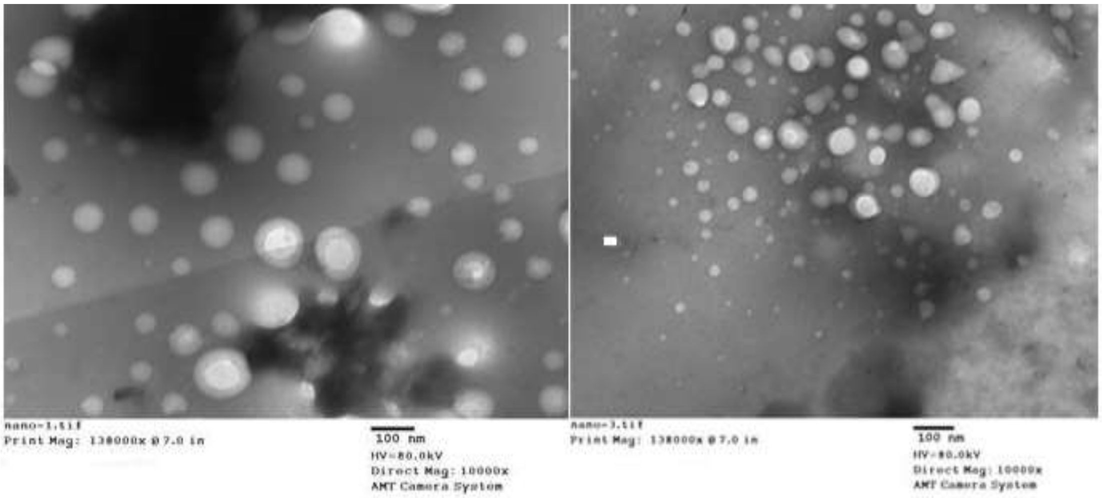

Figure 27: TEM image of optimized batch (F9)

DSC Analysis

The disappearance of endothermic peak of F9 and all other batches of Box-Behnken designed erlotinib loaded chitosan nanoparticles using solvent evaporation method showed that drug may have been dispersed or dissolved in the polymer matrix during the formation of nanoparticles.

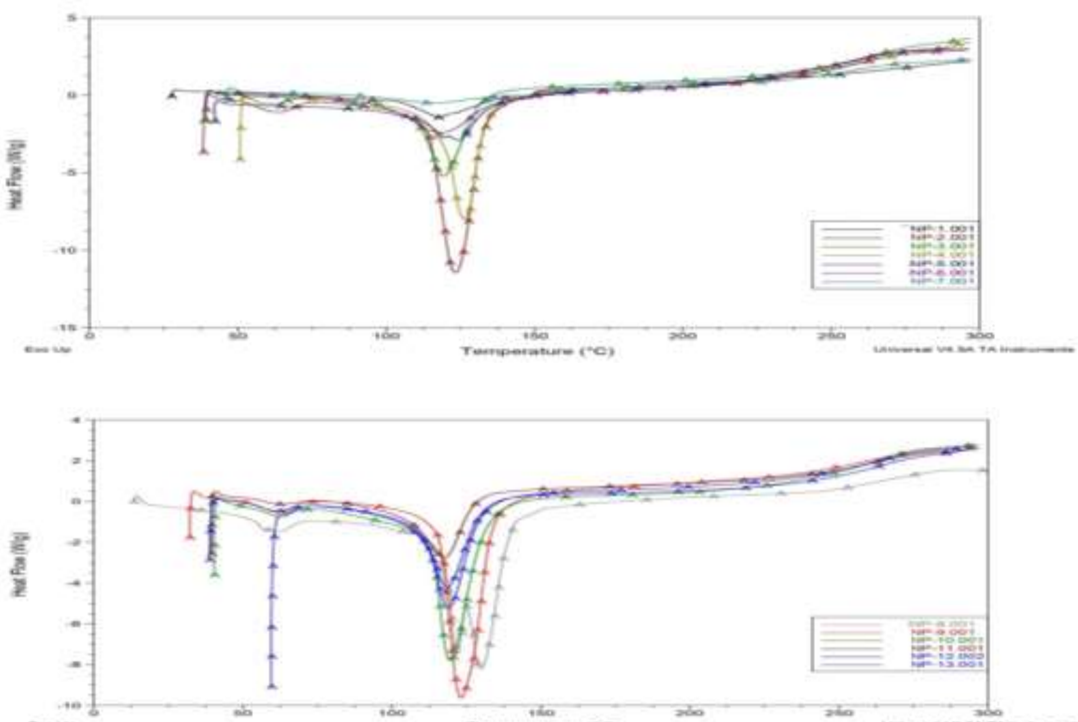

Figure 28: DSC thermograms of the formulations

Release Kinetics Study

The in vitro drug release data of the optimized erlotinib loaded PLGA nanoparticles were fitted to various kinetics model equations such as zero order, first order, Higuchi model and Korsmeyer Peppas model to understand the mechanism of drug release and kinetics of drug release from tablets. The correlation coefficient (R^2) values were obtained for determining the mechanism and kinetics of drug release. Out of all the models, Korsemeyer-Peppas model showed the highest R^2 value for in-vitro release data for F9 obtained in the 0.1N HCl (0.994) followed by Higuchi model (0.986).

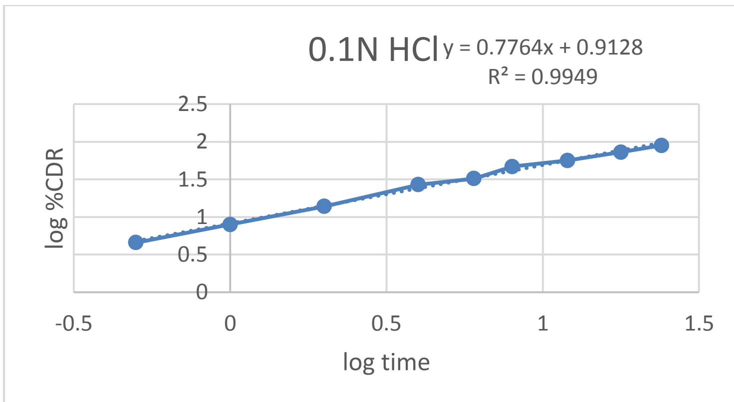

Figure 29: Korsmeyer-Peppas plot of Optimized Formulation (F9)

Stability Studies

Table 9: Stability Result of Formulation

Evaluation Parameter	**Temperature**	**Time (Months)**			
		1st	**2nd**	**3rd**	**6th**
Particle Size (nm)	4°C	108.1	112.4	114.6	120.5
	Room Temperature	109.2	115.8	118.9	126.4
	45°C	113.5	118.7	126.6	130.9
% CDR in 0.1N HCl	4°C	88.36±0.98	87.31±0.91	86.82±0.98	88.36±0.98
	Room Temperature	88.31±0.95	87.15±0.84	86.61±0.95	85.51±0.42
	45°C	88.19±0.92	87.69±0.79	86.49±0.65	85.89±0.56

Comparison with Marketed Formulation

The optimized batch F9 showed 7.93% and 4.55% of drug release in 0.1N HCl and Phosphate Buffer pH 6.8 within 1 h, respectively whereas the marketed formulation showed the release of 80.97% and 28.51% in 0.1N HCl and Phosphate Buffer pH 6.8 within 1 h, respectively. After 24 h, the optimized formulation showed 88.36% and 40.12% of drug release in 0.1N HCl and Phosphate Buffer pH 6.8, respectively, whereas the marketed tablet released 94.35% and 41.22% in 0.1N HCl and Phosphate Buffer pH 6.8 after 24 h, respectively. The optimized nanoparticle formulation F9 released erlotinib slowly in comparison to marketed tablet formulation which may help in improving the therapeutic efficacy of the drug and reducing the side effects of conventional tablet dosage form.

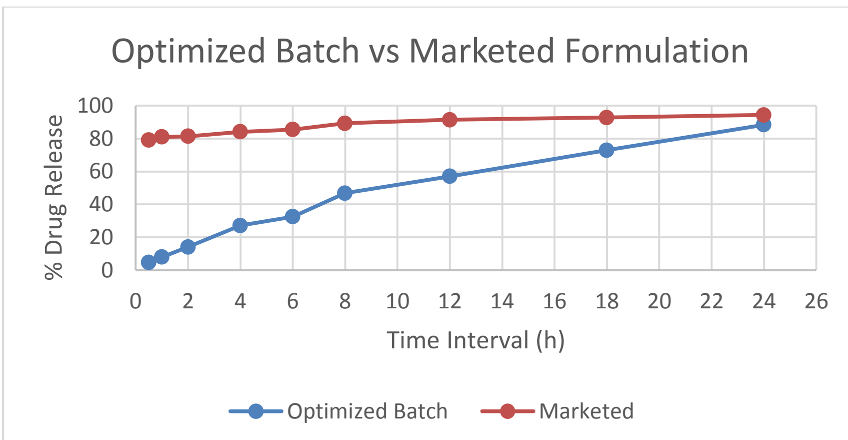

Figure 30: Drug Release of Marketed Formulation and Optimized Formulation F-9 (in 0.1N HCl)

Conclusion

The nanoparticles were prepared by solvent evaporation method using box Behnken software which was found effective enough through which the particle size and polydispersity index were monitored by varying the variables like concentration of polymer, surfactant and sonication time. The optimized nanoparticles were obtained with particle size range which can be effective in prolonging the circulation time of the drug helping in the delivery of the drug at the target site. The mathematical developed models can be used further for the formulation of nanoparticles with the desired characteristics. formulated nanoparticles followed non-fickian mechanism indicating that the release of drug is controlled by the diffusion, erosion and swelling mechanisms. The optimized nanoparticle formulation released erlotinib in a sustained fashion in comparison to the marketed tablet formulation (Erlocip-150).

Future Perspectives

Future research should focus on multiple functions of NPs, such as targeted drug delivery and simultaneous imaging. DDS has been created with the aim of improving the medicinal and therapeutic properties of drugs. They often store the drugs in themselves like a repository. These systems release the drug in the right place and at the right time.

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