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FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLES OF BRIGATINIB

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Abstract:

Treating human non-small cell lung cancer effectively remains a significant challenge due to issues, such as low absorption, frequent dosing, and side effects associated with traditional anti-cancer drugs. This study focuses at solid lipid nanoparticles (SLNs) as a new way to deliver drugs. These nanoparticles could provide better control over how these drugs are absorbed and released in the body, making treatment more manageable for patients. Brigatinib -loaded SLNs were prepared by modified high shear homogenization and ultrasonication method using different concentration of solid lipid (Compritol 888 ATO, Cholesterol) and stabilizers (Tween 80 or Span 20) The physicochemical properties and the in vitro release study for all Brigatinib -loaded SLNs were investigated. The results showed that Brigatinib loaded-SLNs were almost spherical shape having colloidal sizes with no aggregation. The drug entrapment efficiency ranged from 53.25% to near 76.18%. The zeta potential values lie between -25.3and -29.5mV presenting good stability. From the results F6 considered as optimized formulation.

Keywords: *Brigatinib and solid lipid nanoparticles.*

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INTRODUCTION:

Recent years it has become more evident that the development of new drugs alone is not sufficient to ensure progress in drug therapy. I*n vitro* obtained are more exciting but very often followed by disappointing results *in vivo*. Main reasons for this therapy failure include:

- Insufficient drug concentration due to poor absorption, rapid metabolism and elimination (e.g., peptides& proteins),
- Drug distribution to other tissues combined with high drug toxicity (e.g., anticancer drugs),
- Poor drug solubility which excludes i.v. injection of aqueous drug solution,
- High fluctuation of variable plasma levels due to unpredictable bioavailability after peroral administration, including the influence of food on plasma levels (e.g., cyclosporine).

To overcome these biopharmaceutical challenges, versatile formulation approaches are required which will accommodate the physicochemical properties of the individual drug while simultaneously exploiting the physiological environment. Solid lipid nanoparticles have been reported as an alternative drug delivery device to traditional polymeric nanoparticles. SLNs are in submicron size range (50-1000nm) and are composed of physiologically tolerated lipid components. At room temperature the particles are in solid state. These are made of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled release drug-delivery system can be a major advance towards solving these two problems. It is for this reason that the science and technology responsible for development of controlled-release pharmaceuticals has been, and continues to be the focus of a great deal of attention in both industrial and academic laboratories.

1.1. CONVENTIONAL DRUG THERAPY[1]:

To gain appreciation for the value of controlled drug therapy, it is useful to review some fundamental aspects of conventional drug delivery. Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug e.g.: A solution, suspension, capsule tablet etc. can produce a drug blood level versus time profile. The term drug blood levels refer to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. Administration of a drug by either intravenous injection or an extra vascular route, e.g., orally, intramuscularly or rectally does not maintain drug blood levels within the therapeutic range for extended periods of time. The short-duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by for e.g., increasing the initial dose of an intravenous injection, toxic levels can be produced at early times. This approach obviously is undesirable and unsuitable. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple dose therapy.

1. If the dosing interval is appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For e.g., drugs with short half-lives require frequent designs to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient non-compliance with the multiple-dosing regimens can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple dosing can produce the desired drug blood level for extended period of time. Frequently, however these problems are significant enough to make drug therapy with conventional dosage forms less desirable than controlled-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of controlled-release drug delivery systems.

1.2. TERMINOLOGY[2, 3]:

Modified-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustained release

3. Site-specific targeting
4. Receptor targeting.

Delayed-release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form. Examples of delayed release systems include repeat-action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the systems is successful at maintaining constant drug levels in target tissue or cells, it is considered controlled-release systems.

Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissues, for receptor release, the target are the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems.

1.3. ADVANTAGES OF CONTROLLED RELEASE PREPARATIONS:

1. Decreased incidence and/ or intensity of adverse effects and toxicity.
2. Better drug utilization.
3. Controlled rate and site of release.
4. More uniform blood concentrations.
5. Improved patient compliance.
6. Reduced dosing frequency.
7. More consistent and prolonged therapeutic effect.
8. A greater selectivity of pharmacological activity.

1.4. OBJECTIVES[4]:

Control release systems include any drug delivery system that achieves slow release of drug over an extended period of time.

The objectives of oral sustained release formulations are:

1. Frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient.
4. Better control of drug absorption can be attained.

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METHODOLOGY:

Analytical Method Development

Determination of absorption maxima: Absorption maxima is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

Procedure: For the preparation of calibration curve stock solution was prepared by dissolving 100 mg of accurately weighed drug in 100ml of methanol (1mg/ml). Further 1ml of the stock solution was pipette out into a 100 ml volumetric flask and volume was made up with phosphate buffer (6.8 Phosphate Buffer). From this stock solution pipette, out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200-400 nm using double beam UV spectrophotometer. The absorption maxima were obtained at 265 nm with a characteristic peak.

Preparation of calibration curve: It is slightly soluble in water; hence methanol was used for solubilizing the drug. Stock solution (1 mg/mL) of Brigatinib was prepared in methanol and subsequent working standards (5, 10, 15, 20 and 25 µg/ml) were prepared by dilution with phosphate buffer of pH-6.8. These solutions were used for the estimation Brigatinib by UV method. The whole procedure was repeated three times and average peak area was calculated. Calibration plot was drawn between concentrations and peak area. Calibration equation and R^2 value are reported.

Preparation of SLN

Preparation of Brigatinib loaded solid lipid nanoparticles

Drug-loaded solid lipid particles were prepared by hot homogenizing followed by the ultrasonication method. Brigatinib was dispersed during about 10g of mixed lipid phase (consisted of Compritol 888 ATO and Cholesterol) maintained at around 5°C above the melting temperature of mixed lipid and dissolved in a mixture of ethanol. Organic solvents were completely removed employing a rotary flash evaporator. An aqueous phase was prepared by dissolving the stabilizers (Tween 80 or Span 20) in distilled water (sufficient to supply 30ml) and heating to an equivalent temperature of the oil phase. The hot aqueous phase was added to the oil phase and homogenization was performed (at 2500 rpm and 70 °C) employing a mechanical stirrer for 25 minutes. Brigatinib loaded SLN was finally obtained by allowing the recent nano-emulsion to chill at temperature, and was stored at 4°C within the refrigerator.

- Variables for selection of excipients of solid lipid nanoparticles:
  - Compritol 888 ATO (mg)
  - Cholesterol(mg)

Table: Composition of solid lipid nanoparticles formulations (F1 to F9)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Brigatinib	30	30	30	30	30	30	30	30	30
Compritol 888 ATO (%)	0.5	1	1.5	2	0.5	1	1.5	2	0.5
Cholesterol (mg)	0.5	0.7	0.5	0.7	0.5	0.7	0.5	0.7	0.5
Tween 80 (mL)	2	4	6	8	-	-	-	-	1
Span 60 (mL)	-	-	-	-	2	4	6	8	1
Distilled water (ml)	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Ethanol (ml)	10	10	10	10	10	10	10	10	10

Characterization of preparing solid lipid nanoparticles:

Particle Sizes, PDI, Zeta Potential:

The mean particle length and polydispersity index (PDI), that's a degree of the distribution of nanoparticles population, was decided the usage of dynamic light scattering (Delta Nano C, Beckman counter), and Zeta capability becomes anticipated on the premise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS (Malvern Instruments, UK). Samples had been diluted with the distilled water before measurement and measure at a hard and fast angle of 1650c for the particle size and poly dispersity index (PDI) analysis. For the Zeta ability measurement, Samples have been diluted as 1;40 ratio with filtered water (v/v) before analysis. Average particle size, PDI, and zeta potential have been then measured in triplicate.

Drug content:

Brigatinib content in solid lipid nanoparticles was assayed by an UV-visible spectrophotometer. Solid lipid nanoparticles (100mg) were dissolved in 10ml methanol by shaking the mixture for 5 mins. One ml of the resultant solution was taken and diluted to 10ml with methanol. Then, aliquots were withdrawn and absorbance was recorded at 265 nm using UV-visible spectrophotometer (Lab India 3200).

Yield of solid lipid nanoparticles:

After complete drying the solid lipid nanoparticles powders were collected and weighed accurately. The yield of solid lipid nanoparticles was calculated using the formula

$$\text{Percentage yield} = \frac{\text{Total weight of proliposomes}}{\text{total weight of drug} + \text{weight of added materials}} \times 100$$

Entrapment Efficiency:

Entrapment Efficiency (EE) of the Brigatinib loaded SLNs changed into determined by measuring the awareness of uninterrupted drug in an aqueous medium by centrifugation method. The nanoparticles had been centrifuged during a high-space cooling Centrifuge (C-24. Remi) the usage of nano step centrifuge tubes with ultra-filter out having a relative molecular mass cutoff 100KD (Pall existence sciences-India) at 5000rpm for 15min at 4oc, and therefore the supernatant was separated. The amount of Brigatinib inside the supernatant changed into determining the usage of a UV-Visible spectrophotometer (U-1800, Hitachi) at lambda max 265 nm after suitable dilution.

The percent entrapment efficiency (%) changed into calculated by means of the usage of the subsequent formula:

$$\%EE = \frac{\text{Total drug content-Free drug x100}}{\text{Total drug content}}$$

Percent amount of drug release from semi permeable membrane

Franz diffusion cell was used for the in vitro drug release studies. Semi permeable membrane was placed between Donar and receptor chamber of diffusion cell. Receptor chamber was filled with freshly prepared 30ml 5.5 PH phosphate buffer. SLN gel equivalent to 1gm was placed on semi permeable membrane. The Franz diffusion cell was placed over magnetic stirrer (REMI 1ML) with 500rpm and temperature was maintained at 37 ± 1^0C. 5ml of samples were withdrawn periodically and replaced with fresh buffer. The withdrawn samples were periodically diluted and analysed for drug content using UV visible spectrophotometer (Lab India 3200) at 265 nm.



Fig: Drug release from semi permeable membrane

Application of Release Rate Kinetics to Dissolution Data:
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:
To study the zero–order release kinetics the release rate data ar e fitted to the following equation.
F = K o t
Where, 'F' is the drug release at time 't', and 'K o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation
Log (100-F) = kt. A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.
F = k t1/2
Where, 'k' is the Higuchi constant.
In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:
The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

M t / M ∞ = K t n
Where, M t / M ∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (M t / M ∞) versus log (time) is linear.

Fourier Transform Infrared (FTIR) spectroscopy:
The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FT IR analysis of the pure drug and optimized formulation were carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY).

Differential Scanning Calorimetry:
The possibility of any interaction between the drug and the Excipients during preparation of SLN was assessed by carrying out thermal analysis of optimized formulation using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

SEM (Scanning Electron microscope) studies
The surface morphology of the layered sample was examined by using SEM (Hitachi, Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stub. These sample stubs were coated with a thin layer (30Å) of gold by

employing POLARON-E 3000 sputter coater. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.

RESULTS AND DISCUSSION:

CALIBRATION PLOT OF BRIGATINIB IN PHOSPHATE BUFFER OF pH-6.8:

A standard graph of Brigatinib in phosphate buffer of pH 6.8 was plotted using Absorbance and concentration as shown in Table and Fig. Equation for linearity curve and R^2 were calculated as Y=0.0245X +0.007 and R^2 =0.9986. Brigatinib showed maximum absorbance in phosphate buffer (pH 6.8) at 265 nm. The solution obeyed Beer-Lambert's law for concentration range of 5 to 25 µg/mL with regression coefficient of 0.9986. Standard curve of prepared Brigatinib in phosphate buffer pH 6.8 is shown below.

Table: Calibration curve of Brigatinib in phosphate buffer pH 6.8.

Concentration (µg/mL)	Absorbance
0	0
5	0.128
10	0.265
15	0.381
20	0.487
25	0.619

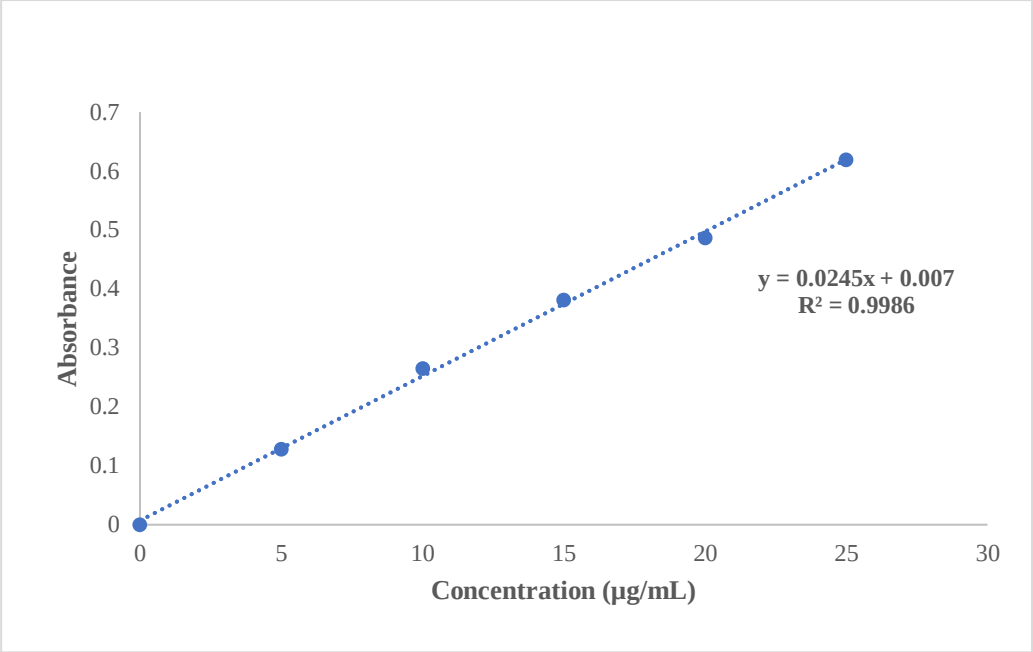

Fig: Calibration curve of Brigatinib in phosphate buffer pH 6.8

Characterization of Solid lipid nanoparticles:

Table: Percentage yield, Drug Content, Entrapment Efficiency of all solid lipid nanoparticles formulations

FORMULATION	Percentage yield	Drug Content	Entrapment Efficiency
F1	85.15	91.09	62.90
F2	90.21	92.15	72.63
F3	93.05	95.63	89.12
F4	92.19	96.12	53.25
F5	94.09	97.56	63.02
F6	**96.11**	**98.60**	**76.18**
F7	87.92	93.93	62.82
F8	91.36	95.10	70.14
F9	94.39	96.50	74.96

Percentage yield of formulations F1 to F9 by varying drug to lipid ratio was determined and is presented in Table. Highest drug content, Highest Entrapment efficiency observed for F6 formulation.

Table: Particle Sizes, PDI, Zeta Potential of all solid lipid nanoparticles formulations

FORMULATION	Particle Size (nm)	PDI	Zeta Potential (mV)
F1	178.1	0.097	-25.3
F2	165.9	0.090	-26.4
F3	158.5	0.160	-27.6
F4	170.2	0.181	-25.9
F5	154.4	0.105	-28.4
F6	**142.0**	**0.089**	**-29.5**
F7	176.2	0.149	-28.5
F8	153.0	0.125	-25.8
F9	149.4	0.120	-25.4

The particle size of the all formulations was observed in the range of 142.0 to 178.1. The less particle size, PDI observed in the F6 formulation i.e., 0.089 nm respectively. The Zeta potential ranges from -25.3 mV to -29.5mV to all the formulations. The negative charge on the surface of the Nanoparticle is believed to facilitate uptake from the intestine by the Payers patch, leading to the lymphatic circulation, also it is believed to prevent entangling of the nanoparticles in the negatively charged mucous owing to the repulsion of like charges.

Table: *In vitro* dissolution studies of F1-F9 SLN formulations in percentage

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	17.60	10.01	9.05	12.08	15.13	12.36	14.10	13.39	12.38
2	20.19	18.26	15.15	18.26	21.02	18.29	19.63	18.60	18.29
4	28.63	24.39	21.36	23.39	27.83	32.41	26.12	23.24	23.71
6	40.12	35.25	28.11	29.89	32.10	40.09	37.69	30.96	32.92
8	56.30	44.79	32.49	37.20	39.42	46.11	48.14	37.14	38.49
10	60.12	57.93	42.19	42.96	50.90	54.39	57.26	46.25	46.58
12	67.75	65.30	57.58	70.20	71.35	67.14	63.30	50.63	58.26
18	76.30	73.12	66.36	75.14	79.63	78.25	70.12	58.22	69.15
24	84.14	80.29	70.91	83.79	89.05	94.99	76.56	70.56	76.87
48	87.05	84.41	75.49	93.36	95.21	**98.36**	90.71	86.10	80.62

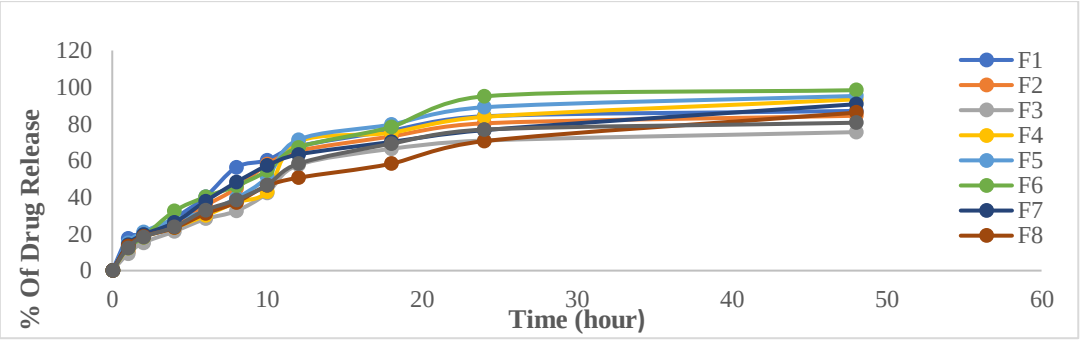

Fig: *In vitro* dissolution studies of F1-F9 SLN formulations in percentage

In vitro drug release study of the selected nanoparticles (F1, F2, F3, F4, F5, F6, F7, F8 and F9) was carried out. The nanoparticles exhibited 48 hours sustained release pattern. 18.29 of the incorporated amounts of drugs were found to be released during the first 2 hours, followed by a slowed release of 98.36 % of the drug up to 48 hours. The Brigatinib - loaded nanoparticles R6 showed a better release profile of 98.36% by 48 hours. The prolonged release at 48 hours can be attributed to slow diffusion of drug from polymer matrix. The results of *in vitro* drug release are depicted in above Table.

Release Kinetics

To analyze the drug release mechanism the *in vitro* release was fitted into various release equations and kinetic models first order, zero order, Higuchi and Korsmeyer-Peppas. The release kinetics of optimized formulation F6 (Compritol 888 ATO) is shown in Table and in following Figures.

Table: Release kinetics of optimized formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
12.36	1	1.000	1.092	0.000	1.943	12.360	0.0809	-0.908	87.64	4.642	4.442	0.200
18.29	2	1.414	1.262	0.301	1.912	9.145	0.0547	-0.738	81.71	4.642	4.339	0.302
32.41	4	2.000	1.511	0.602	1.830	8.103	0.0309	-0.489	67.59	4.642	4.073	0.568
40.09	6	2.449	1.603	0.778	1.777	6.682	0.0249	-0.397	59.91	4.642	3.913	0.729
46.11	8	2.828	1.664	0.903	1.732	5.764	0.0217	-0.336	53.89	4.642	3.777	0.864
54.39	10	3.162	1.736	1.000	1.659	5.439	0.0184	-0.264	45.61	4.642	3.573	1.069
67.14	12	3.464	1.827	1.079	1.517	5.595	0.0149	-0.173	32.86	4.642	3.203	1.439
78.25	18	4.243	1.893	1.255	1.337	4.347	0.0128	-0.107	21.75	4.642	2.791	1.850
94.99	24	4.899	1.978	1.380	0.700	3.958	0.0105	-0.022	5.01	4.642	1.711	2.930
98.36	48	6.928	1.993	1.681	0.215	2.049	0.0102	-0.007	1.64	4.642	1.179	3.462

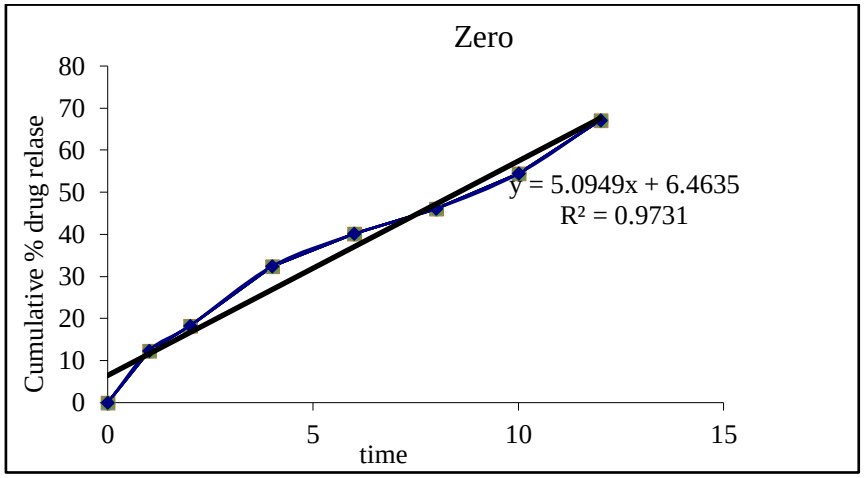

Figure: Zero order release kinetics

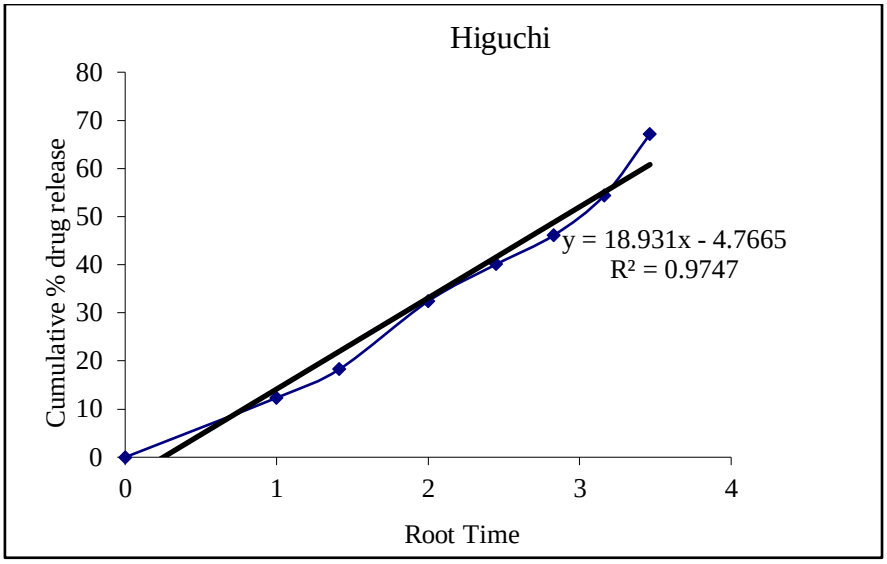

Figure: Higuchi release kinetics

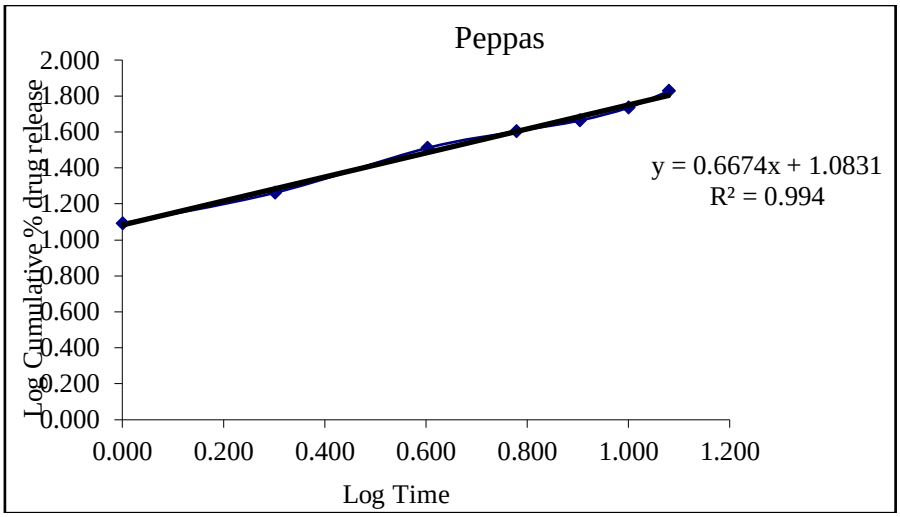

Figure: Peppas release kinetics

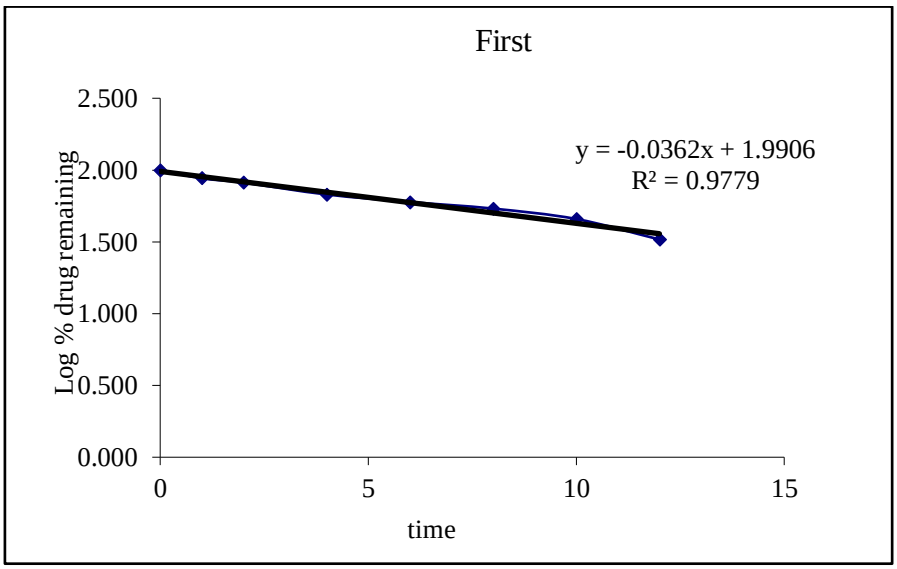

Figure: First order release kinetics

The prepared F6 optimized Compritol 888 ATO nanoparticles were subjected to the drug release kinetics and release mechanism. The formulations were studied by fitting the drug release time profile with the various equations such as Zero order, First order, Higuchi and Korsmeyer pappas. The optimized formulation F6 optimized Chitosan a Nanoparticle was analyzed for the drug release mechanism. The best correlation coefficient value (0.994) indicates the best release mechanism (First order).

FTIR

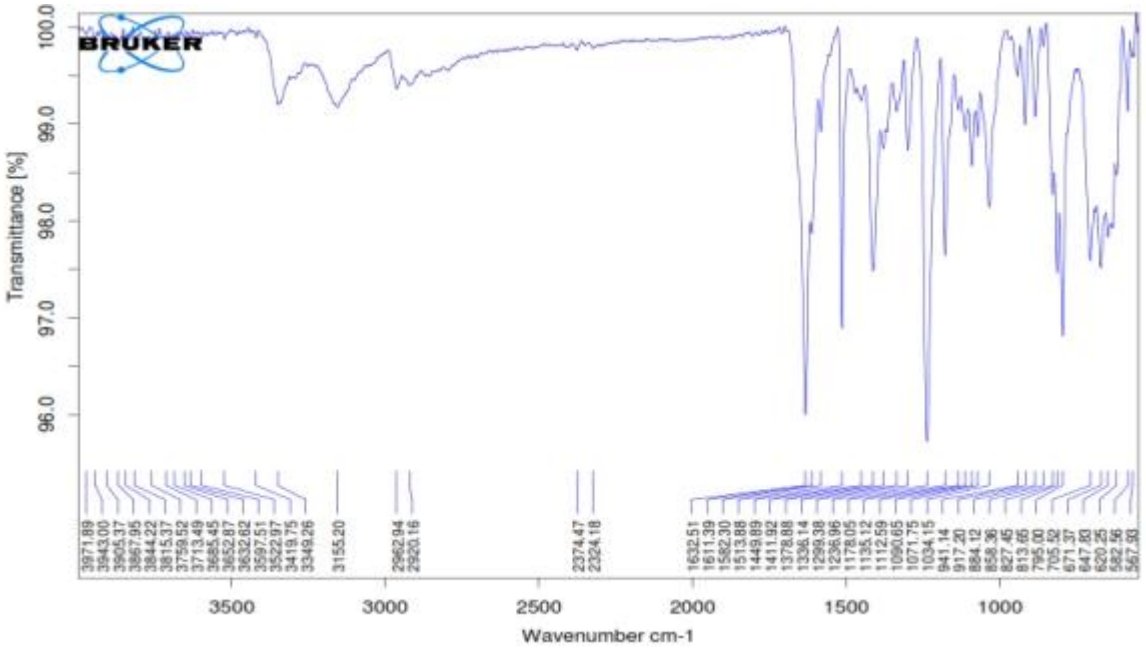

Figure: Brigatinib Pure drug FTIR

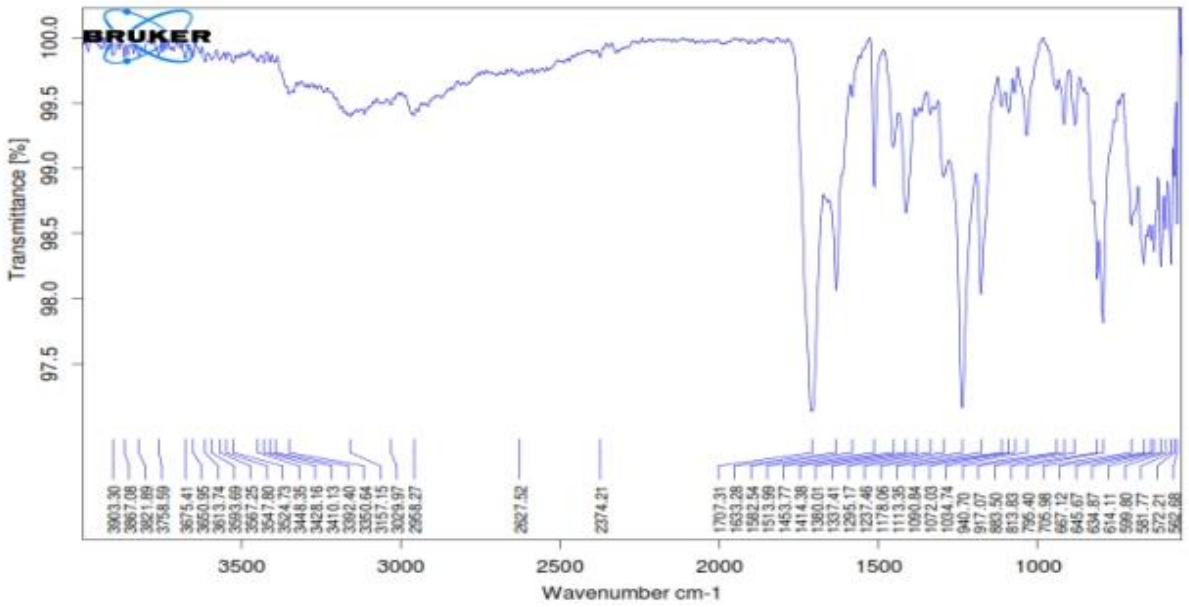

Figure: Brigatinib optimized FTIR

Infrared studies were carried out to confirm the compatibility between the lipid, drug, and selected excipients. From the spectra it was observed that there was no major shifting, as well as, no loss of functional peaks between the spectra of the drug and drug-loaded SLN. This indicated no interaction between the drug and other excipients.

DSC:

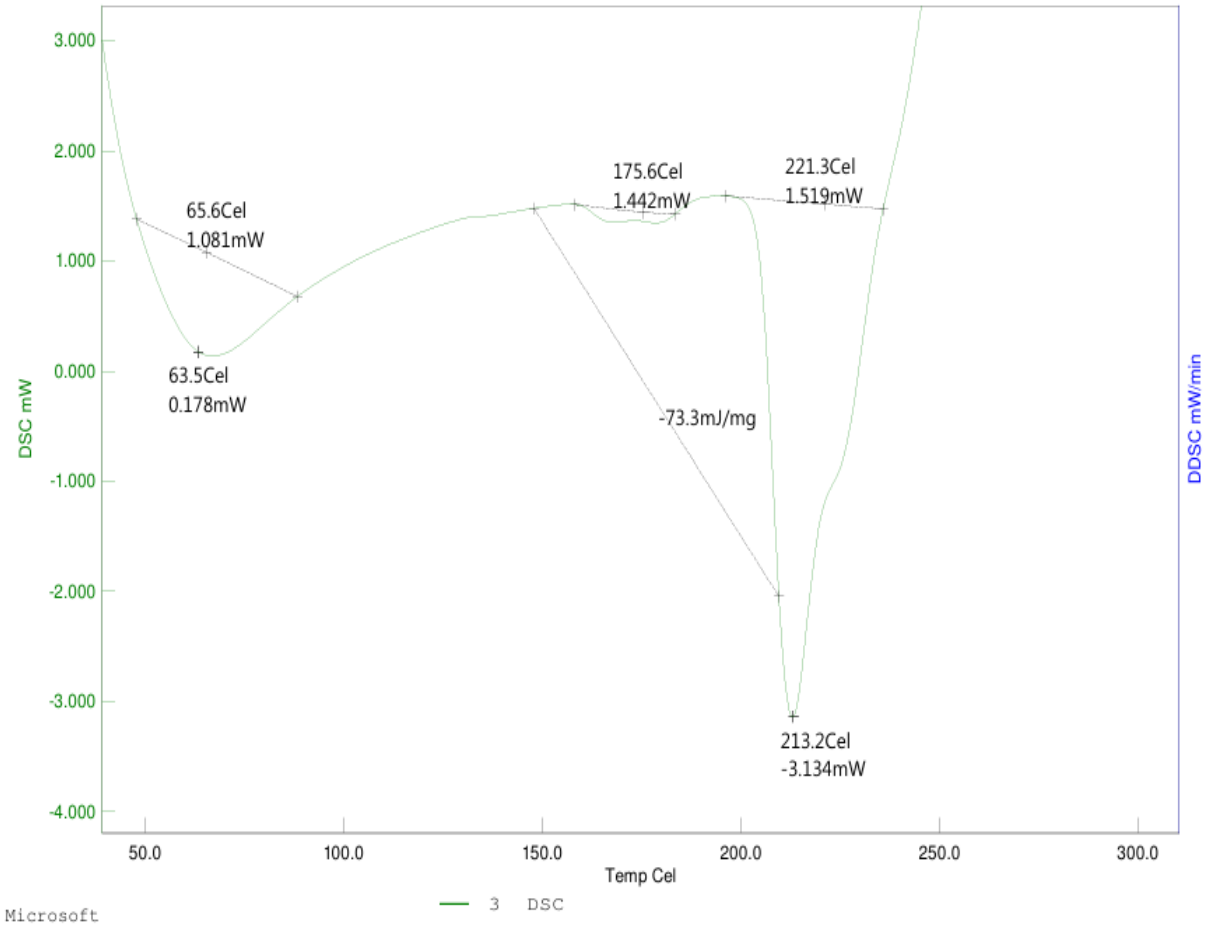

Figure: Brigatinib optimized

DSC curve of optimized formulation showed, the pure drug shows that it is in crystalline anhydrous state, exhibiting a sharp exothermic peak at 214 °C, corresponding to its melting point Search Results 213.2°C), and for the formulation peaks are observed at 213.2°C.

XRD

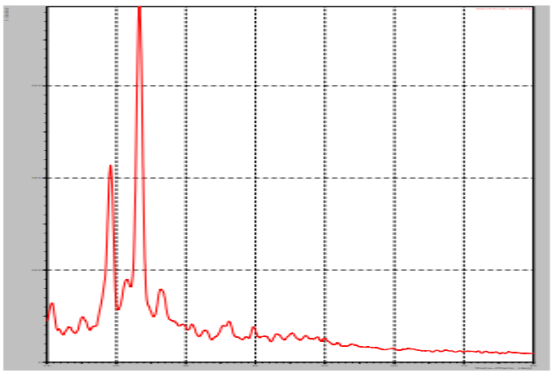

Figure: XRD Brigatinib F6 nanoparticles

SEM

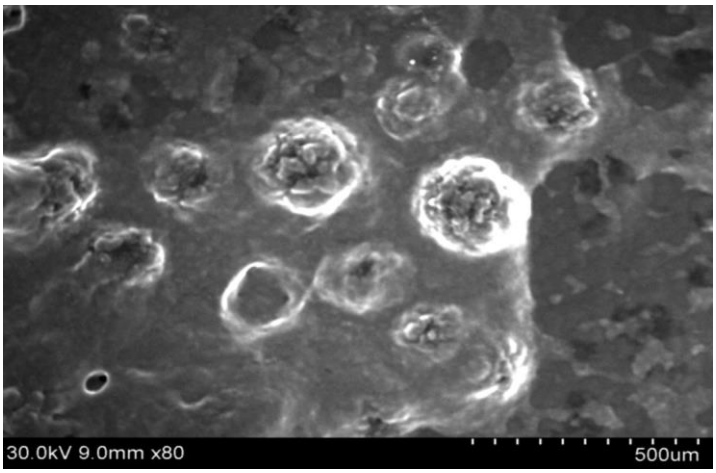

Figure: Brigatinib optimized

SEM studies showed that the Brigatinib - loaded solid lipid nanoparticles had a spherical shape with a smooth surface as shown in Figure.

CONCLUSION:

Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissues, for receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and areal so considered to be controlled drug-delivery systems.

Colloid drug-delivery systems are used to increase the bioavailability of drug substance, to improve drug stability, to sustain and control drug-release rates, to target drugs to specific sites in the body and to stimulate the immune system. Encapsulation within a colloidal system can protect these therapeutic agents from degradation and deliver them to their sites of action.

Solid lipid nano particles have been reported as an alternative drug delivery device to traditional polymeric nanoparticles. SLNs are in submicron size range (50-1000nm) and are composed of physiologically tolerated lipid components. At room temperature the particles are in solid state. These are made of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs.

The compatibility between pure drug and optimised were detected by FTIR (Bruker Alpha-T) spectra.

Among all the formulation F6 considered as best formulation. Among all the formulations F6 with Compritol 888 ATO (1%), Cholesterol (0.7 mg) showed the drug release of 98.76% in 48 hours and was selected as the ideal formulation. The less particle size, PDI observed in the F6 formulation i.e., 142.0nm, 0.089 respectively. It had highest zeta potential value hence stable formulation. The data revealed a better fit to the First order model.

Sustained release of drug from gel maintained the drug concentrations for longer time. These results confirmed the permeation of formulations through the rat abdominal and could be permeate through the human skin.

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