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Formulation and Optimisation of Repotrectinib Nanoparticles

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G. Deepika[1], K. Jyothi[2], A.Yasodha[3]

[1]*Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001 India.*

[2] *Associate Professor, Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001 India.*

[3]*Professor & Principal, Department of Pharmaceutical Analysis, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001 India.*

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ABSTRACT

The goal of this study was to assess the efficacy of a method based on the creation of nanoparticles as an innovative formulation of Repotrectinib with enhanced therapeutic efficacy. Repotrectinib has low solubility and permeability, which result in limited and variable bioavailability; its low stability makes it difficult to develop stable aqueous liquid formulations. The Repotrectinib nanoparticles were created using the solvent evaporation process. The numerous formulations with varied drug-polymer and surfactant ratios were analyzed and improved. Repotrectinib nanoparticles containing PLGA were created using the solvent evaporation method, and then the particle size was decreased by sonication. Particle size, surface morphology by SEM, drug excipient compatibility by FTIR, and in-vitro drug release experiments were used to characterize the produced nanoparticles. The formulation with the best encapsulation efficiency was (F-3) a drug encapsulation effectiveness of up to 92.85 % has been attained in this study. It was discovered that the efficiency of encapsulation improved along with the polymer content. According to the results of the current investigation, the manufacture of Repotrectinib Polymeric nanoparticles can be done using a solvent evaporation process followed by sonication.

INTRODUCTION

Nanotechnology Nanotechnologies can be defined as the design, characterization, fabrication and application of structures by controlling morphology and dimension at a nanometer scale.[1] Nanotechnology offers unique approaches to revolutionary impact on biology and medicine because of size dependent physical and chemical properties. Among the approaches for exploiting nanotechnology in diagnostics and therapeutics, nanoparticles offer some unique advantages as sensing, image improvement, and antimicrobial agents. Therefore nanoparticles (NPs) used for parenteral, oral, ocular and transdermal application and sustained released formulations.[2] Nanotechnology has gained huge attention over time. The fundamental component of nanotechnology is the nanoparticles. Nanoparticles are particles between 1 and 100 nanometres in size and are made up of carbon, metal, metal oxides or organic matter.[3] The nanoparticles exhibit unique physical, chemical and biological properties at nanoscale compared to their respective particles at higher scales. Repotrectinib is used to treat ROS1-positive non-small cell lung cancer (NSCLC) that has spread within your chest or to other parts of the body.[4]

MATERIALS

Repotrectinib was obtained from Alkem Pvt Mumbai, PLGA and Poloxamer procured from SD fine chemicals Mumbai. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Compatibility Study (IR spectroscopy)

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.[5]

Method of Preparation of Repotrectinib Loaded Nanoparticles:

Formulation Development

Loaded polymeric nanoparticles were prepared using PLGA as a polymer, poloxamer 407, and sodium lauryl sulfate (SLS) as a stabilizer utilizing the solvent evaporation method. PLGA concentration was kept constant (10 mg), while poloxamer 407, SLS, and drug were used in varying concentrations. The developed nanoformulations were characterized for their

physicochemical properties, drug loading, % entrapment efficiency, and stability. The optimized nanoformulations were then decorated with Repotrectinib.[6]

Table-1: Composition of the Nanoparticles

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Repotrectinib	20	20	20	20	20	20	20	20
PLGA	5	10	15	20	5	10	15	20
Poloxamer 407	0.5	1	1.5	2	2.5	3	3.5	4
SLS	5	5	5	5	5	5	5	5
Methanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of Repotrectinib Loaded Polymeric Nanoparticles:

Particle Size:

All of the generated batches of nanoparticles were observed under a microscope to establish their sizes. The average size of the nanoparticles was determined by measuring the size of each batch's nanoparticles in a small drop of nanoparticle dispersion on a slide.[7]

SEM Analysis

The morphology of nanoparticles was examined using the scanning electron microscope (SEM, Hitachi, and Tokyo, Japan). After being properly diluted (1:100) in double-distilled water, Repotrectinib -freeze-dried SLNs were added to a drop of the nanoparticle formulation and left to air dry. The sample was then observed under various magnifications and a 15,000 volt accelerating voltage. The imaging was performed in a high vacuum.[8]

Drug Encapsulation Efficiency:

A set volume of the nanoparticles dispersion (10 ml) was poured into a centrifuge tube at room temperature, and it was spun at 18,000 rpm for 20 minutes (Remi Instruments Pvt Ltd, India). The drug's absorbance in the supernatant was measured spectrophotometrically at a maximum wavelength of 291 nm after the lipid component was removed (Shimadzu 1800, Japan).[9]

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount entrapped}}{\text{Total drug loaded}} \times 100$$

In-Vitro Drug Release Studies:

Utilizing the dialysis bag approach, in vitro release tests were carried out. Prior to the release trials, the dialysis membrane (molecular weight cutoff between 12,000 and 14,000) was immersed in double distilled water for an overnight period. As releasing media, phosphate buffer pH 7.4 was also employed. A donor compartment and a receptor compartment make up the experimental unit. A boiling tube that was cut open at one end and tied with a dialysis membrane at the other end serves as the donor compartment, into which 3 ml of polymeric dispersion was injected for the release research. The receptor compartment is made up of a 250 ml beaker that contains 100 ml of release media and was kept at a temperature of 37 0.5 °C. Every 3 ml sample was taken out of the receiver compartment and replaced with the same amount of release medium at the 1, 2, 3, 4, 5, 6, 7 and 8h time periods. The collected samples were appropriately diluted before being examined at 291 nm with a UV-visible spectrophotometer.[10]

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug

Da = The amount of drug released

Drug Release Kinetics: [11]

The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Korsmeyer Peppas model (equation 4).

I) Zero Order Kinetics:

$$R = Ko\ t \qquad \text{-- (1)}$$

R=cumulative percent drug

Ko=zero order rate constant

Ii) First Order Kinetics

$$\log C = \log Co - K_1 t / 2.303 \quad \text{-- (2)}$$

Where C = cumulative percent drug

K_1= first order rate constant

iii) Higuchi Model

$$R = K_H \, t^{0.5} \quad \text{-- (3)}$$

Where R = cumulative percent drug

K_H = Higuchi Model Rate Constant

Iv) Korsmeyer Peppas Model:

$$M t / M \alpha = K_k t^n$$

$$\log M t / M \alpha = \log K_k + n \log t \quad \text{-- (4)}$$

Where K_k = Korsmeyer Peppas rate constant

'M t / M α' is the fractional drug, n = diffusional exponent, which characterizes the mechanism of drug.

Stability Studies:

Over the course of 90 days, the stability of Repotrectinib nanoparticle dispersion in screw-capped glass vials was assessed. Four samples were split into two groups and kept at 4°C and 25°C, respectively. At the end of the 90 days, the amount of drug leaking from nanoparticles and the average particle size of the samples were calculated.[12]

RESULTS AND DISCUSSION

Drug - Excipient Compatibility Studies (FT-IR)

Using the FTIR peak matching approach, the compatibility of the medicine with the chosen polymer and other excipients was assessed. The drug-polymer mixture showed no peaks that

appeared or vanished, indicating that there was no chemical interaction between the medication, polymer and other molecules.

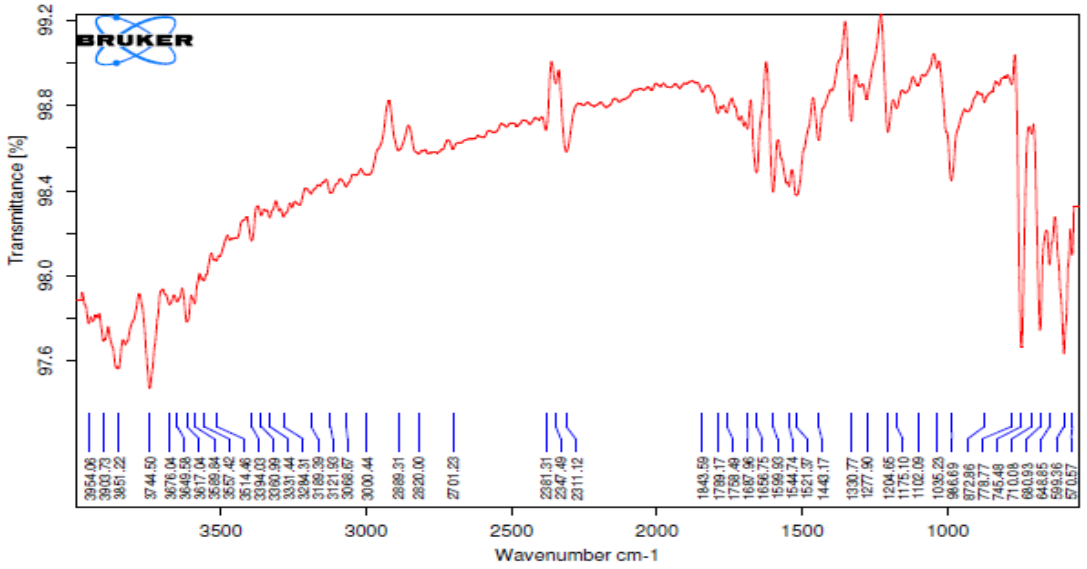

Fig-1: FTIR Spectra of Pure Drug

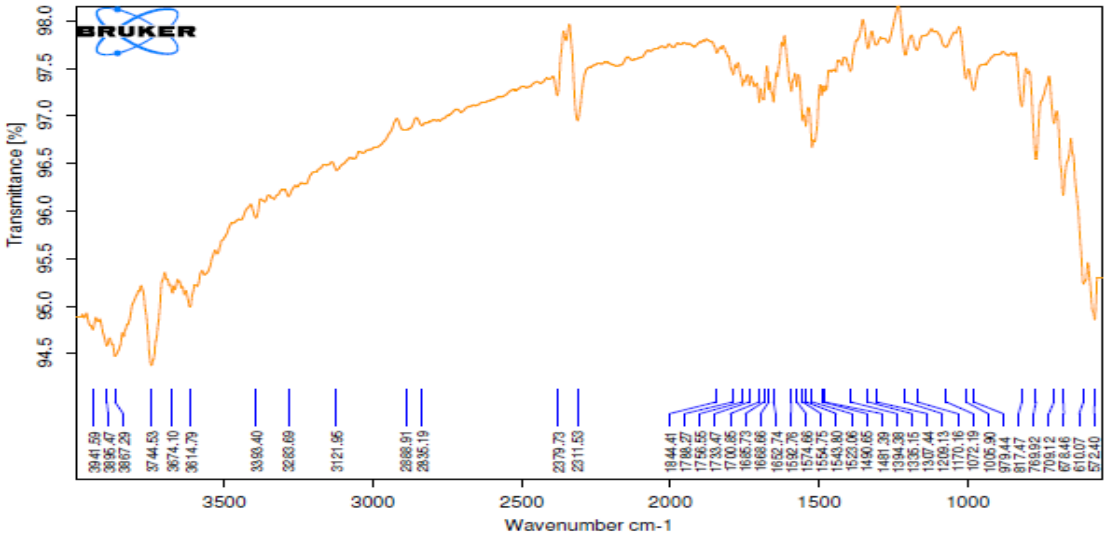

Fig-2: FTIR Spectra of Physical Mixture of Drug and Excipients

EVALUATION PARAMETERS

Particle Size:

With an increase in lipid concentration, the particle size increased. Based on entrapment effectiveness and particle size distribution.

Determination of Zeta Potential:

Zeta potential is a measure of charge present on the vesicle surface. It was determined by using phase analysis light scattering with Malvern Zetasizer at field strength of 20V/cm in distilled water and based on electrophoretic mobility of charged particles present in the Nano carrier system. Charged particles were attracted to the electrode with the opposite charge when an electric field is applied.

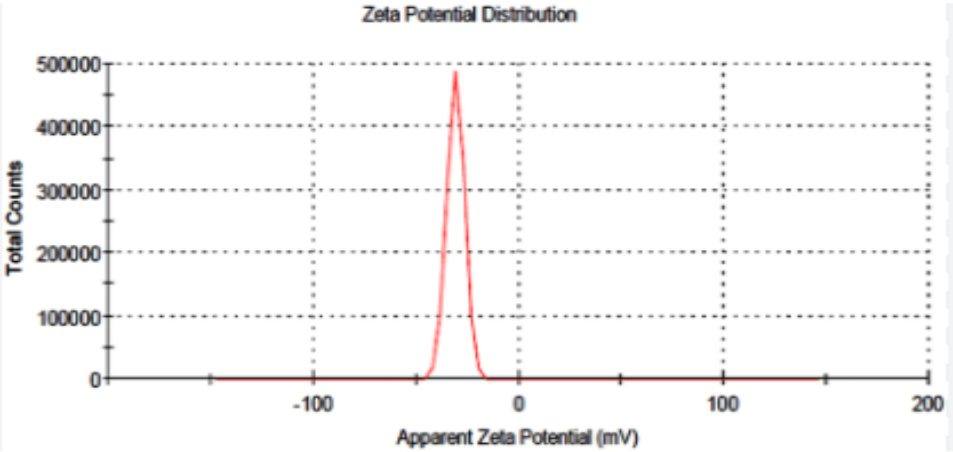

Fig-3: Zeta Potential of Optimized Formulation

The addition of membrane additives affects zeta potential value depending on the type of membrane additives. Zeta potential of optimized Doxorubicin Zno nanoparticles formulation was measured and found to 24- mv. The obtained result of the zeta potential of the prepared formulation indicates particles in the formulation remains suspended and so were found to be stable.

Particle Size

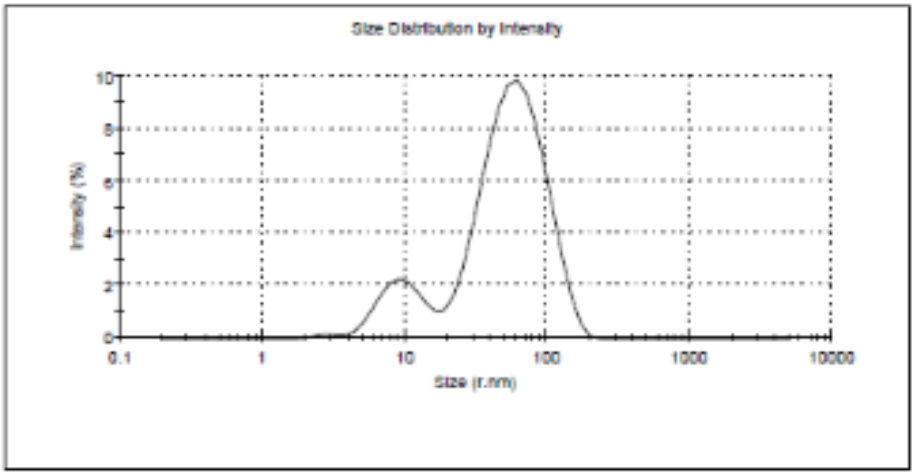

Fig-4: Particle Size of Optimized Formulations

The surfaces of the nanoparticles were smooth.

Surface Morphology:

According to scanning electron microscopy (SEM), the polymeric nanoparticles were round, smooth, and free of any aggregation.

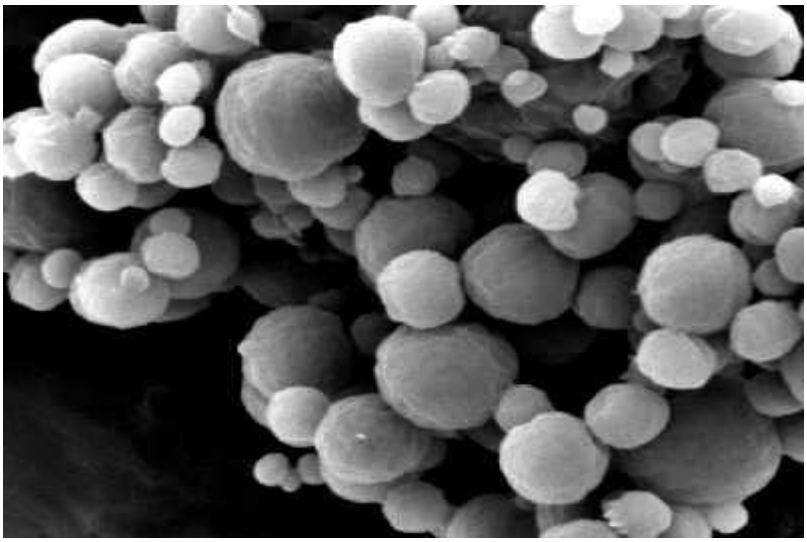

Fig-5: SEM Analysis of Optimized Polymeric Nanoparticle

Drug Entrapment Efficiency:

Optimizing the polymer concentration to be used in the creation of polymeric nanoparticles was the first step of the work plan. Based on the particle size and entrapment effectiveness of the discovered polymeric nanoparticles, the polymer content was optimized.

Table-2: Evaluation Studies of Prepared Polymeric Nanoparticles: Entrapment Efficiency and Particle Size and Zeta Potential

Batch No.	Particle size (nm)	Entrapment Efficiency (%)	Zeta Potential
F1	243	75.86	-30
F2	241	78.12	-28
F3	270	73.92	-17
F4	256	75.20	-19
F5	274	77.14	-20
F6	290	79.85	-24
F7	276	76.82	-26
F8	268	71.25	-29

In Vitro Drug Release Studies

Using a dialysis membrane and a pH 7.4 buffer, the in vitro diffusion investigations were carried out for eight hours. The initial release of the medication from all three batches was discovered to be between 25 and 30 percent in 8 hours. This resulted from the drug's release from the surface of the nanoparticles. Later, for 8 hours, a consistent and gradual medication release was seen. The polymer ratio in the F6 formulation was shown to be the most effective one.

Table-3: *In Vitro* Drug Release Profiles of Repotrectinib Polymeric Nanoparticles (F1-F8)

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	15.98	14.71	14.89	15.81	16.82	17.10	15.93	16.10
2	28.90	27.82	27.56	27.57	28.93	24.69	29.63	28.51
3	37.46	35.60	34.68	32.54	33.25	35.10	38.40	37.19
4	48.19	47.92	48.25	47.90	46.80	45.89	48.81	45.66
5	53.64	52.38	55.74	52.20	53.69	55.50	56.93	50.35
6	68.90	67.91	69.86	65.94	64.77	69.98	65.89	66.98
7	78.17	80.40	78.90	77.51	80.13	81.25	83.25	80.19
8	91.68	92.86	93.58	94.18	95.82	97.10	95.32	94.56

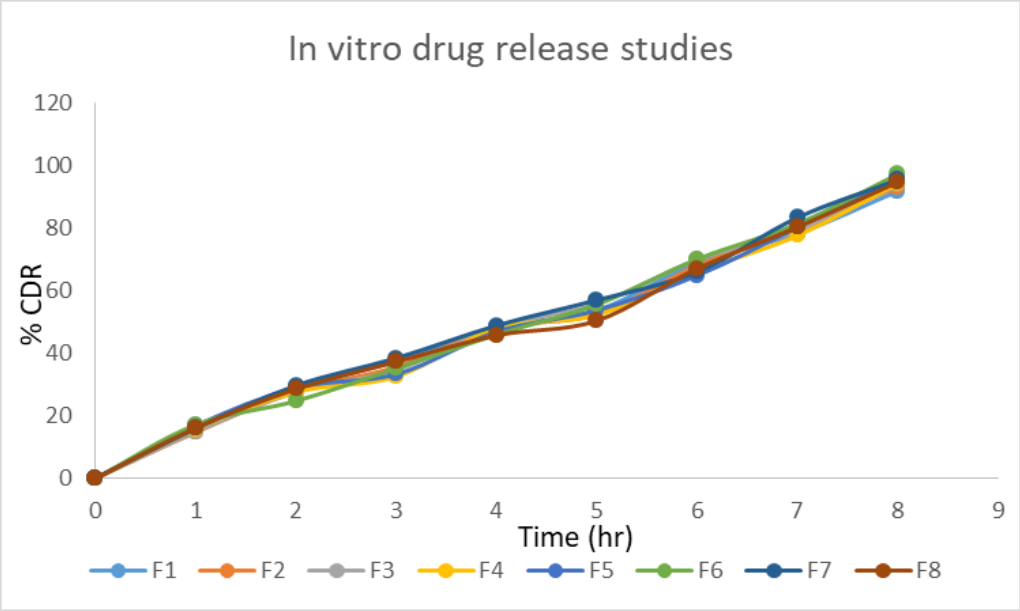

Fig-6: Drug Release for all Formulations

Drug Release Kinetics

Table-4: Drug Release Kinetics of Optimized Formulation

TIME	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	0	0
1	17.1	1	0	1.23299611	82.9	1.91855453
2	24.69	1.41421356	0.30103	1.39252109	75.31	1.87685265
3	35.1	1.73205081	0.47712	1.54530712	64.9	1.8122447
4	45.89	2	0.60206	1.66171806	54.11	1.73327753
5	55.5	2.23606798	0.69897	1.74429298	44.5	1.64836001
6	69.98	2.44948974	0.77815	1.84497394	30.02	1.47741069
7	81.25	2.64575131	0.8451	1.90982337	18.75	1.27300127
8	97.1	2.82842712	0.90309	1.98721923	2.9	0.462398

Zero Order Kinetics

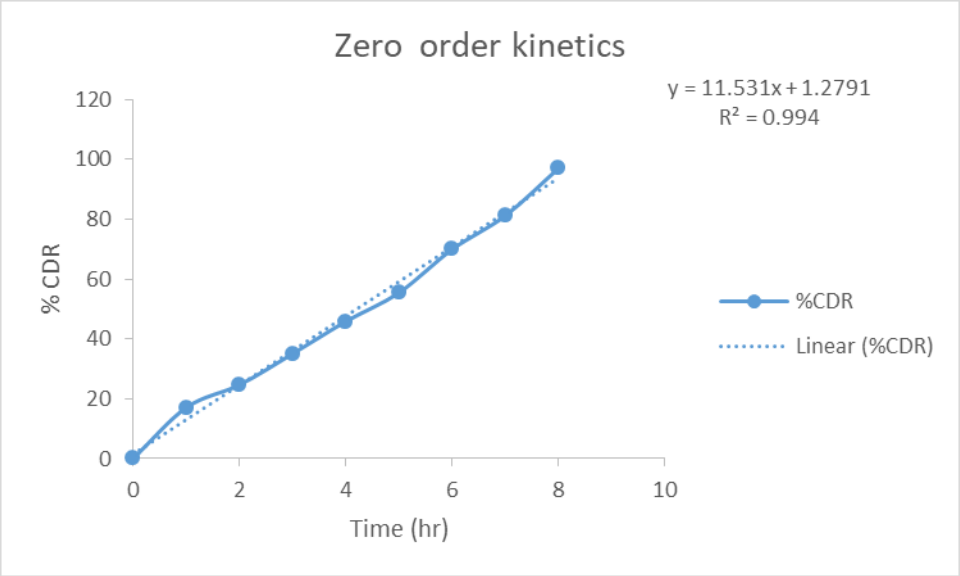

Fig-7: Zero Order Kinetics of Optimized Formulation

First Order Kinetics

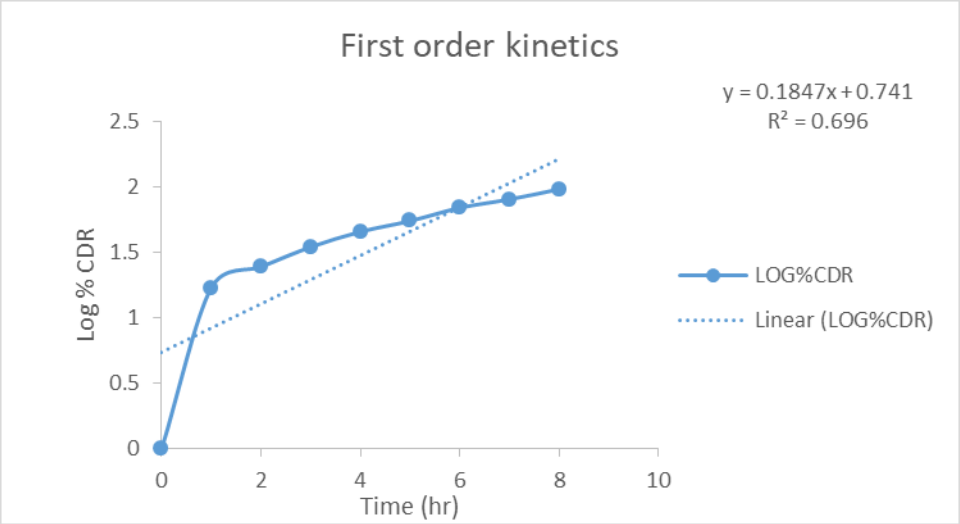

Fig-8: Zero Order Kinetics of Optimized Formulation

Higuchi Model

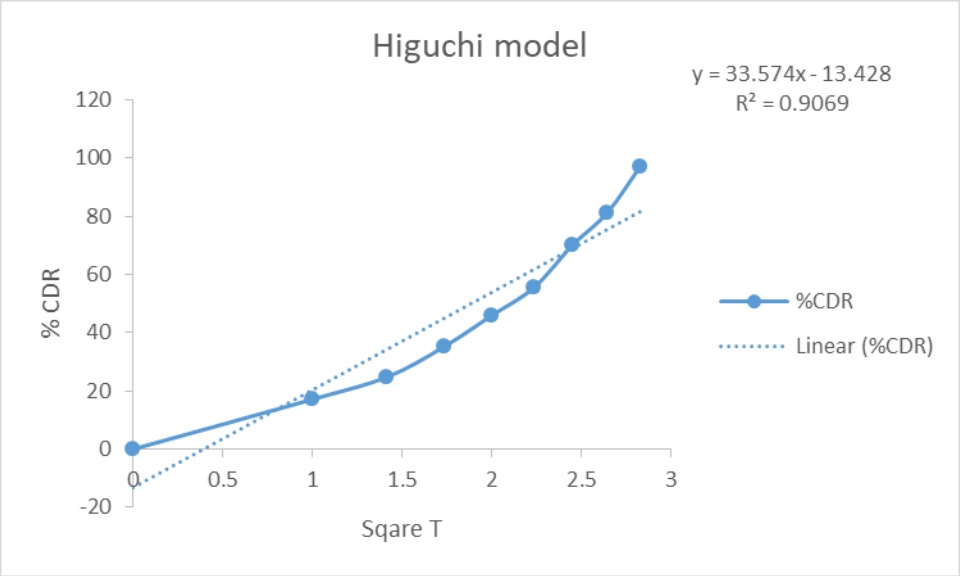

Fig-9: Higuchi Model of Optimized Formulation

Korsmeyer Peppas

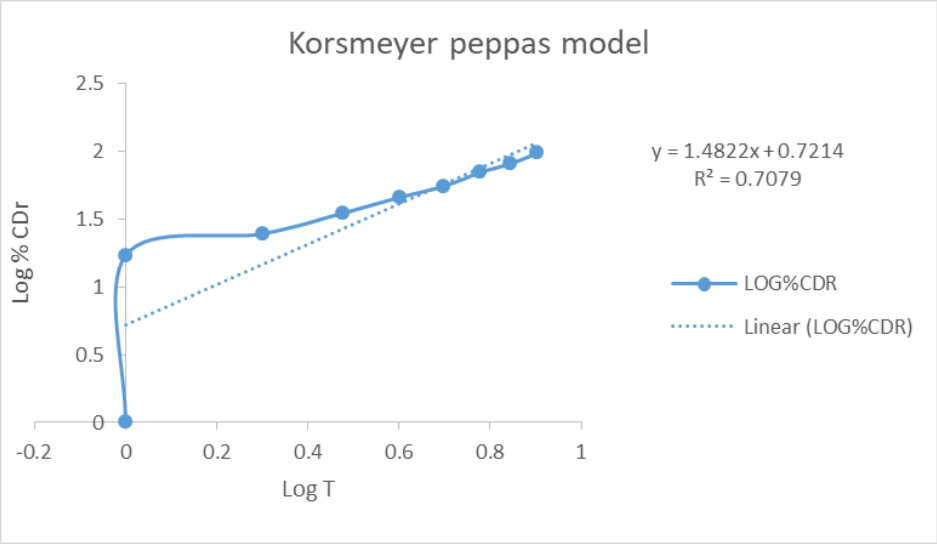

Fig-10: Korsmeyer Peppas of optimized formulation

The release kinetics for all the prepared nanoparticles was evaluated to determine the release behaviour of Repotrectinib from the prepared nanoparticles. The release data were analyzed with zero-order kinetic, first-order kinetic, and Korsmeyer–Peppas kinetic models, as well as the Higuchi kinetic model. It was revealed that the release data from nanoparticles s fit to

Higuchi kinetic model with the highest (r) value, while for free Cisplatin nanoparticles, the release data fit the zero order kinetic model.

Stability Studies:

After three months, the physical and chemical characteristics of the nanoparticles of formulation F-6 had not significantly changed. The parameters quantified at various times were displayed.

Table-5: Results of Stability Studies of Optimized Formulation F-6

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	**25^{0}C/60%RH % Release**	97.10	96.85	95.81	94.86	**Not less than 85 %**
F-6	**30^{0}C/75%RH % Release**	97.10	96.21	95.25	94.10	**Not less than 85 %**
F-6	**40^{0}C/75%RH % Release**	97.10	96.08	95.46	94.02	**Not less than 85 %**

CONCLUSION

The current study suggested a unique Repotrectinib nanoparticle formulation for regulated release. Investigation into the polymeric nanoparticles' production, characterization, and in-vitro release was done. The numerous formulations with varied drug-polymer and surfactant ratios were analysed and improved. A drug encapsulation effectiveness of up to 79.85 % has been attained in this study. Repotrectinib nanoparticles containing polymers were created using the solvent evaporation method, and then the particle size was decreased by sonication. Formulations using polymeric nanoparticles performed well in terms of medication content and encapsulation effectiveness. This shows that the formulation procedure was suitable and reproducible in nature, and it provided a good yield. The formulation with the best encapsulation efficiency was (F-6) It was discovered that the percentage of encapsulation efficiency along with the polymer concentration. According to the method described, permeation studies with dialysis membrane were conducted. The in vitro drug release profiles of all the formulations indicated an initial burst effect, followed by a gradual drug release. The formulations demonstrated good drug release from the polymer. These polymeric nanoparticles contained more Repotrectinib and released it more quickly.

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 **Author -1**	G. Deepika – Corresponding Author Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001
Image Author -2	K. Jyothi Associate Professor, Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001
Image Author -3	A.Yasodha Professor & Principal, Department of Pharmaceutical Analysis, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001