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Preparation and Evaluation of Ivosidenib Nanoparticles

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Abstract: Polymeric nanoparticles are a promising novel drug delivery system and have advantages in abnormal lipids therapy. Ivosidenib is an Antineoplastic Agent that is used in the treatment of a acute myeloid leukemia and locally advanced or metastatic cholangiocarcinoma therapy. The aim of the present study was to prepare and evaluate novel polymeric nanoparticles containing Ivosidenib. The objective of the present study was to formulate and evaluate polymeric nanoparticles of Ivosidenib byEmulsification sonication method using Sodium alginate, Chitosan and Ethyl cellulose as a polymer. The nanoparticles were characterized for FTIR, particle size, poly-dispersity index, entrapment efficiency (EE), zeta potential, morphological study, DSC and *invitro* study. Infrared studies showed that there was no drug excipients interaction. Negative values of zetapotential indicated the good stabilization of the prepared nanoparticles.

Nine formulations of Ivosidenibnanoparticles were prepared using Emulsification sonication method. The particles sizes and zeta potential were measured using zeta-plus analyzer. The particle morphology was also studied using scanning electron microscopy (SEM). The *in-vitro* release of the drug from the nanoparticles was carried out in phosphate buffer saline pH 6.8.

The particle sizes of the prepared NPs were in nano size which ranged from (140.5 to 173.9nm) with positive zeta potential. The drug entrapment efficiency was varied with the drug polymer ratio from 52.30% to 76.25%. The SEM showed uniform shape and regularly distributed particle sizes. The *in-vitro* drug release study exhibited the sustained release of Ivosidenibwith burst release. The cumulative percentage released after 12 hr. were between were 80.62 and 99.13%.

The studies, therefore, indicate the successful formulation development of NPs with distinctly improved bioavailability potential and can be used as drug carrier for sustained or prolonged drug release.

Key words: Ivosidenib, Emulsification sonication method, Sodium alginate, Chitosan, Ethyl cellulose and Nanoparticles.

1. INTRODUCTION:

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 [1]. The nanoparticles exhibit a unique physical, chemical and biological properties at nanoscale compared to their respective particles at higher scales. This phenomena is due to a

relatively larger surface area to the volume, increased reactivity or stability in a chemical process, enhanced mechanical strength, etc. [2]. These properties of nanoparticles has led to its use various applications. The nanoparticles differs from various dimensions, to shapes and sizes apart from their material [3]. A nanoparticle can be either a zero dimensional where the length, breadth and height is fixed at a single point for example nano dots, one dimensional where it can possess only one parameter for example graphene, two dimensional where it has length and breadth for example carbon nanotubes or three dimensional where it has all the parameters such as length, breadth and height for example gold nanoparticles.

The nanoparticles are of different shape, size and structure. It be spherical, cylindrical, tubular, conical, hollow core, spiral, flat, etc. or irregular and differ from 1 nm to 100 nm in size. The surface can be a uniform or irregular with surface variations. Some nanoparticles are crystalline or amorphous with single or multi crystal solids either loose or agglomerated. Numerous synthesis methods are either being developed or improved to enhance the properties and reduce the production costs. Some methods are modified to achieve process specific nanoparticles to increase their optical, mechanical, physical and chemical properties. A vast development in the instrumentation has led to an improved nanoparticle characterisation and subsequent application. The nanoparticles are now used in every objects like from cooking vessel, electronics to renewable energy and aerospace industry. Nanotechnology is the key for a clean and sustainable future.[4]

Advantages of nanoparticles

Nanoparticles offer numerous advantages in drug delivery system. These advantages include, but are not limited:

- Nanoparticles have many significant advantage over conventional and traditional drug delivery system.
- Nanoparticles are control and sustain release form at the site of localization, they alter organ distribution of drug compound. They enhance drug circulation in blood, bioavailability, therapeutic efficacy and reduce
- Nanoparticles can be administer by various routes including oral, nasal, parenteral, intra-ocular etc.
- In the tiny areas of body nanoparticles shows better drug delivery as compare to other dosage form and target to a particular cell type or receptor.
- Due to small particle size nanoparticles overcome resistance by physiological barriers in the body and easily penetrates to cell walls, blood vessels, stomach epithelium and blood–brain barrier.
- Nanoparticle enhance the aqueous solubility of poorly soluble drug, which improves bioavailability of drug.
- As a targeted drug carrier nanoparticles reduce drug toxicity and enhance efficient drug distribution.
- By using polymers drug release form nanoparticles can be modified which makes polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives and antibiotics.
- Useful to diagnose various diseases
- Enhanced stability of ingredients
- Prolonged shelf life
- Used in dental surgery also as filling the tiny holes in teeth.
- Change the method of drug delivery to improve customer acceptance or reduce manufacturing costs.[5-8]

Limitations of Nanoparticles

a) Small size and large surface area can lead to particleparticle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.

b) In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available.[9,10]

Classification of Nanoparticles

The nanoparticles are generally classified into the organic, inorganic and carbon based.

Organic nanoparticles

Dendrimers, micelles, liposomes and ferritin, etc. are commonly knows the organic nanoparticles or polymers. These nanoparticles are biodegradable, non-toxic, and some particles such as micelles and liposomes has a hollow core (Figure1), also known as nanocapsules and are sensitive to thermal and electromagnetic radiation such as heat and light. These unique characteristics makes them an ideal choice for drug delivery. The drug carrying capacity, its stability and delivery systems, either entrapped drug or adsorbed drug system determines their field of applications and their efficiency apart from their normal characteristics such as the size, composition, surface morphology, etc. The organic nanoparticles are most widely used in the biomedical field for example drug delivery system as they are efficient and also can be injected on specific parts of the body that is also known as targeted drug delivery.

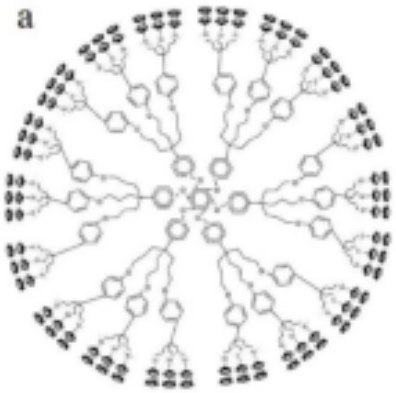

Fig 1.1: Organic nanoparticles

Inorganic nanoparticles

Inorganic nanoparticles are particles that are not made up of carbon. Metal and metal oxide based nanoparticles are generally categorised as inorganic nanoparticles

Metal based. Nanoparticles that are synthesised from metals to nanometric sizes either by destructive or constructive methods are metal based nanoparticles. Almost all the metals can be synthesised into their nanoparticles. The commonly used metals for nanoparticle synthesis are aluminium (Al), cadmium (Cd), cobalt (Co), copper (Cu), gold (Au), iron (Fe), lead (Pb), silver (Ag) and zinc (Zn). The nanoparticles have distinctive properties such sizes as low as 10 to 100nm, surface characteristics like high surface area to volume ratio, pore size, surface charge and surface charge density, crystalline and amorphous structures, shapes like spherical and cylindrical and colour, reactivity and sensitivity to environmental factors such as air, moisture, heat and sunlight etc.

Metal oxides based. The metal oxide based nanoparticles are synthesised to modify the properties of their respective metal based nanoparticles, for example nanoparticles of iron (Fe) instantly oxidises to iron oxide (Fe_2O_3) in the presence of oxygen at room temperature that increases its reactivity compared to iron nanoparticles. Metal oxide nanoparticles are synthesised mainly due to their increased reactivity and efficiency. The commonly synthesised are Aluminium oxide (Al_2O_3), Cerium oxide (CeO_2), Iron oxide (Fe_2O_3), Magnetite (Fe_3O_4), Silicon dioxide (SiO_2), Titanium oxide (TiO_2), Zinc oxide (ZnO). These nanoparticles have possess an exceptional properties when compared to their metal counterparts.

Carbon based

The nanoparticles made completely of carbon are knows as carbon based. They can be classified into fullerenes, graphene, carbon nano tubes (CNT), carbon nanofibers and carbon black and sometimes activated carbon in nano size.

Fullerenes. Fullerenes (C_{60}) is a carbon molecule that is spherical in shape and made up of carbon atoms held together by sp^2 hybridization. About 28 to 1500 carbon atoms forms the spherical structure with diameters up to 8.2 nm for a single layer and 4 to 36 nm for multi-layered fullerenes.

Graphene. Graphene is an allotrope of carbon. Graphene is a hexagonal network of honeycomb lattice made up of carbon atoms in a two dimensional planar surface. Generally the thickness of the graphene sheet is around 1 nm.

Carbon Nano Tubes (CNT). Carbon Nano Tubes (CNT), a graphene nanofoil with a honeycomb lattice of carbon atoms is wound into hollow cylinders to form nanotubes of diameters as low as 0.7 nm for a single layered and 100 nm for multi-layered CNT and length varying from a few micrometres to several millimetres. The ends can either be hollow or closed by a half fullerene molecule.

Carbon Nanofiber. The same graphene nanofoils are used to produce carbon nanofiber as CNT but wound into a cone or cup shape instead of a regular cylindrical tubes.

Carbon black. An amorphous material made up of carbon, generally spherical in shape with diameters from 20 to 70 nm. The interaction between the particles is so high that they bound in aggregates and around 500 nm agglomerates are formed.[11-14]

METHODOLOGY

Characterization of Ivosidenib

Organoleptic properties:

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of Ivosidenib Melting point

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

Determination of Ivosidenib Solubility

Determination of solubility of drug by visual observation. An excess quantity of Ivosidenib was taken separately and add in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

Analytical Method Development

Determination of absorption maxima: Absorption maxima are 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 (pH 6.8). 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 242 nm with a characteristic peak.

Preparation of calibration curve: It is soluble in Methanol; hence Methanol was used for solubilizing the drug. Stock solution (1 mg/mL) of Ivosidenib was prepared in Methanol and subsequent working standards (10, 20, 30, 40 and 50 µg/mL) were prepared by dilution with phosphate buffer of pH-6.8. These solutions were used for the estimation Ivosidenib 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 nanoparticles

Preparation of Ivosidenib loaded nanoparticles

Ivosidenib loaded Nanoparticle was prepared by previously reported emulsification sonication method. Ivosidenib was dissolved in organic solvent (10 ml, methanol). Polymers in different concentrations were dissolved in water. The organic phase was added drop wise into the polymeric solution for emulsification. Then the dispersion was sonicated (20 min) with the application of ultra-probe sonication (60 W/cm^3, Hielscher, Ultra-sonics, Germany). The formulation was stirred at 1500 rpm for 6 h using a magnetic stirrer to evaporate the organic solvent. The prepared NPs were centrifuged at 15,000 rpm for 20 min at 4 °C

(Remi, Mumbai, India). NPs were separated and lyophilized using cryoprotectant (Mannitol 0.2%) and stored for further evaluation.

Table 7.1: Composition of nanoparticles formulations (F1 to F9)

Excipients	I1	I2	I3	I4	I5	I6	I7	I8	I9
Ivosidenib	250	250	250	250	250	250	250	250	250
Sodium alginate (%)	1	1.5	2	-	-	-	-	-	-
Chitosan (mg)	-	-	-	1	1.5	2	-	-	-
Ethyl cellulose	-	-	-	-	-	-	1	1.5	2
Tween 80 (mL)	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
Distilled water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Dichloromethane (ml)	15	15	15	15	15	15	15	15	15
Methanol: Acetone Ratio	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3

Characterization of 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:

Ivosidenib content in nanoparticles was assayed by an UV-visible spectrophotometer. 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 242 nm using UV-visible spectrophotometer (Lab India 3200).

Yield of nanoparticles:

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

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

EntrapmentEfficiency:

Entrapment Efficiency (EE) of the Ivosidenib loaded 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 Ivosidenib inside the supernatant changed into determining the usage of a UV-Visible spectrophotometer (U-1800, Hitachi) at lambda max 242nm 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 242 nm.

Fig: Drug release from semi permeable membrane

Powder X-ray Diffraction (PXRD) Studies

The prepared mixtures were also analyzed using X-ray powder diffractometer (PXRD) which confirms the formation of the new solid phases. The difference in the 2 theta lines confirms the formation of the new solid phases as no two solids have same 2 theta lines, thus revealing the formation of new solid phases. It also reveals the informationabout thecrystal structure, chemical composition, andphysical propertiesof thematerial andalso helpsin structural characterization. This technique detectschanges inthe crystal lattice and istherefore apowerful toolfor studyingpolymorphism, pharmaceuticalsalts, andcocrystalline phases. Spectra of PXRD were taken on a sample stage Spinner PW3064. The samples wereexposed tonickel filtrateCukœ radiations (40 KV, 30 mA) and were scanned from 10° to 40°, 2Ɵ ata stepsize of 0.045° andstep timeof 0.5 s.

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).

***In Vitro* Release Studies**

Drug release was determined by dialysis method; two ml of each formulation (test and control) were poured into dialysis bags and put into 25 ml phosphate buffer (pH 6.8) and stirred (100 rpm, room temperature). At predetermined time intervals, 2 ml of phosphate buffer was taken and then substituted by fresh phosphate buffer. Finally, the amounts of released Simvastatin in phosphate buffer were measured by spectrophotometer at 242 nm. Aliquots withdrawn were assayed at each time interval for the drug released at λ max of 245 nm using UV-Visible spectrophotometer by keeping phosphate buffer pH 6.8 as blank and the amount of released drug was estimated by the standard curve.

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 stubs. 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

Organoleptic properties

Table 8.1: Organoleptic properties

S NO.	Properties	Results
1	State	Solid
2	Colour	White
3	Odour	Odorless
4	Melting point	155°C

Solubility studies

Table 8.2: Solubility studies of drug in different solvents

S NO.	Solvents	Solubility of Ivosidenib
1	Ethanol	Freely soluble
2	DMSO	Freely soluble

CALIBRATION PLOT OF IVOSIDENIB PHOSPHATE BUFFER OF pH -5.5:

A standard graph of Ivosidenibin phosphate buffer of pH-5.5 was plotted using Absorbance and concentration as shown in Table and Fig. Equation for linearity curve and R^2 were calculated as Y=0.0163X+0.0095 and R^2 =0.9993. Ivosidenibshowed maximum absorbance in phosphate buffer (pH 5.5) at 242 nm. The solution obeyed Beer-Lambert's law for concentration range of 10 to 50µg/mL with regression coefficient of 0.9993 Standard curve of prepared Ivosidenibin phosphate buffer pH 5.5 is shown below.

Table 8.3: Calibration curve of Ivosidenib in phosphate buffer pH 5.5

Concentration(µg/mL)	Absorbance
0	0
10	0.178
20	0.348
30	0.491
40	0.662
50	0.821

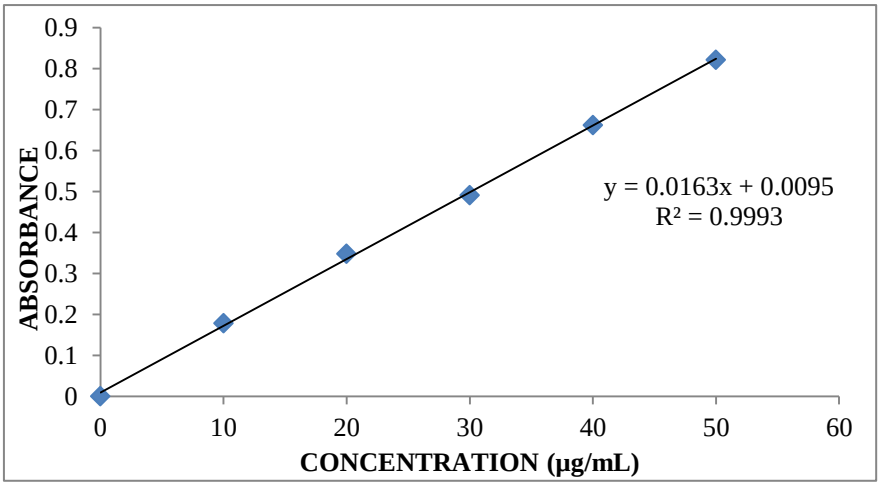

Fig 8.1: Calibration curve of Ivosidenib in phosphate buffer pH 5.5

Characterization of nanoparticles:

Table 8.4: Percentage yield, Drug Content, Entrapment Efficiency of all nanoparticle's formulations

FORMULATION	Percentage yield	Drug Content	Entrapment Efficiency
I1	84.01	91.09	62.16
I2	87.15	92.16	72.33
I3	93.01	95.36	90.56
I4	90.74	96.20	52.30
I5	94.10	97.92	61.22
I6	96.09	98.10	76.25
I7	87.12	93.12	61.02
I8	91.35	93.02	70.85
I9	92.11	96.05	73.25

Percentage yield of formulations I1 to I9 by varying drug to polymer was determined and is presented in Table. Highest drug content, Highest Entrapment efficiency observed for I6 formulation.

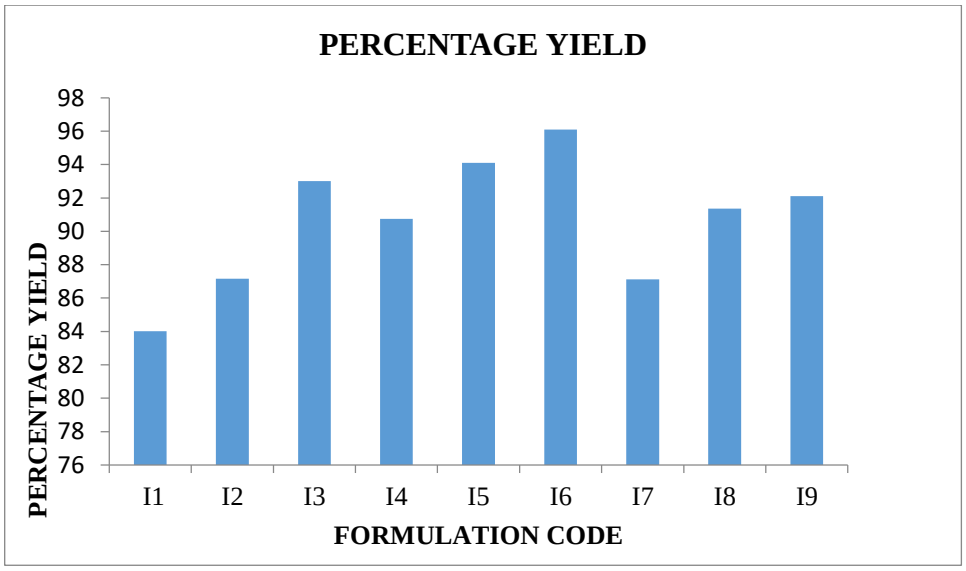

Fig 8.2: Percentage yield of all nanoparticles

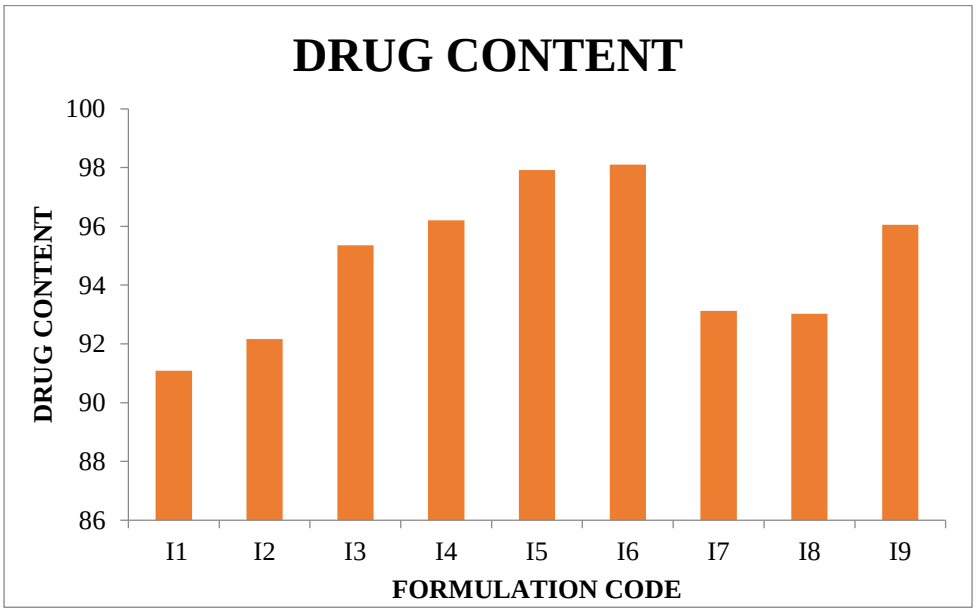

Fig 8.3: Drug Content yield of all nanoparticles

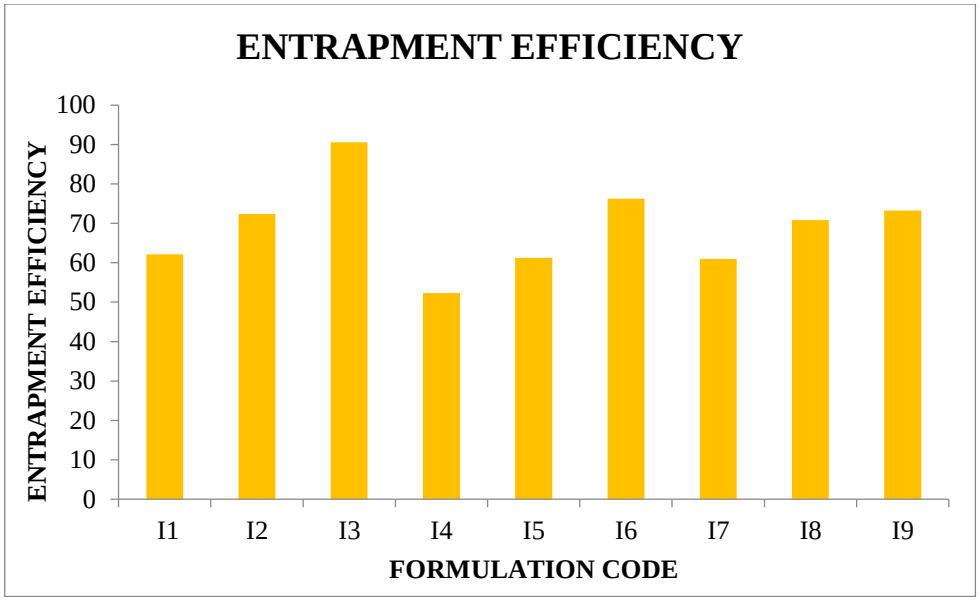

Fig 8.4: Entrapment Efficiency of all nanoparticles

Table 8.5: Particle Sizes, PDI, Zeta Potential of all nanoparticle's formulations

FORMULATION	Particle Size (nm)	PDI	Zeta Potential (mV)
I1	175.9	0.095	-25.3
I2	162.2	0.092	-26.4
I3	156.2	0.162	-27.6
I4	168.5	0.185	-25.9
I5	151.9	0.109	-28.4
I6	140.5	0.090	-29.5
I7	173.9	0.159	-28.5
I8	152.2	0.132	-25.8
I9	148.3	0.123	-25.4

The particle size of the all formulations was observed in the range of 140.5 to 173.9. The less particle size, PDI observed in the F6 formulation i.e., 0.090 nm respectively. The Zeta potential range 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.

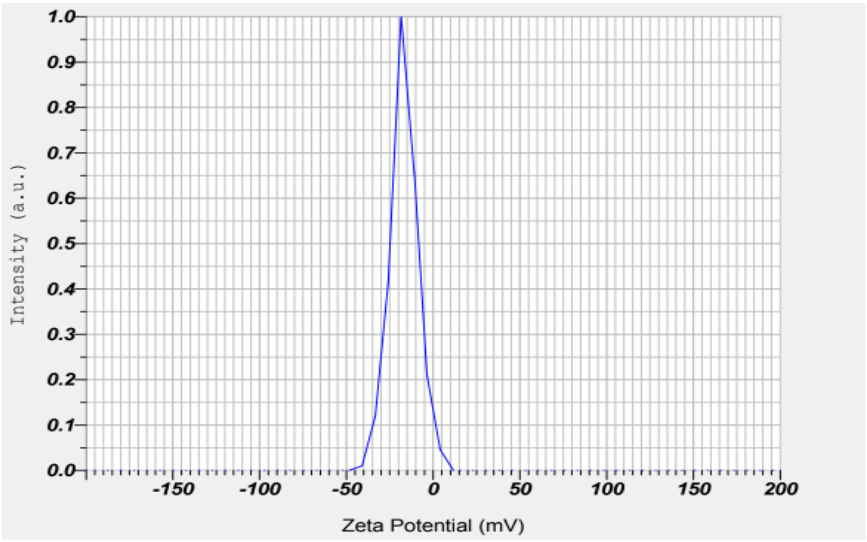

Fig 8.5: Zeta potential of R6 Formulation

DSC:

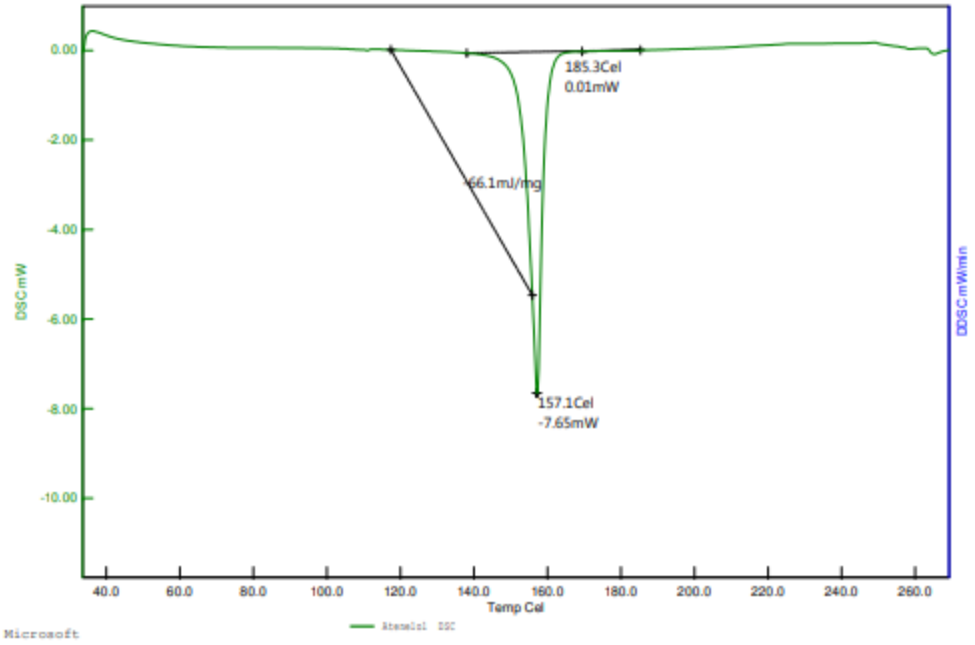

Fig 8.6: IvosidenibPure

SEM

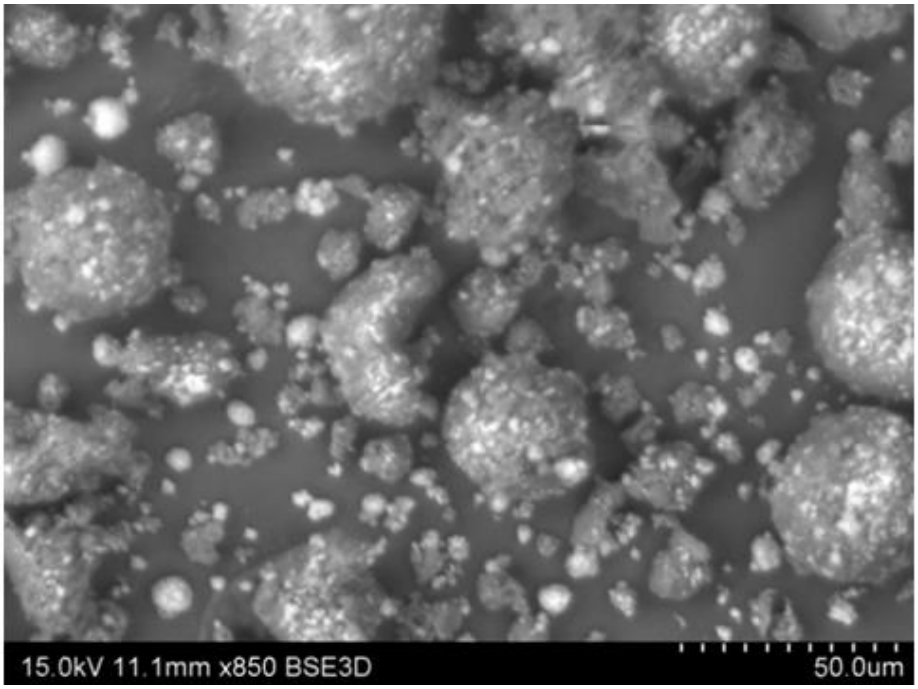

Fig 8.7: IvosidenibI6 optimized nanoparticles

SEM studies showed that the Ivosidenib- loaded nanoparticleshad a spherical shape with a smooth surface as shown in Figure.

XRD

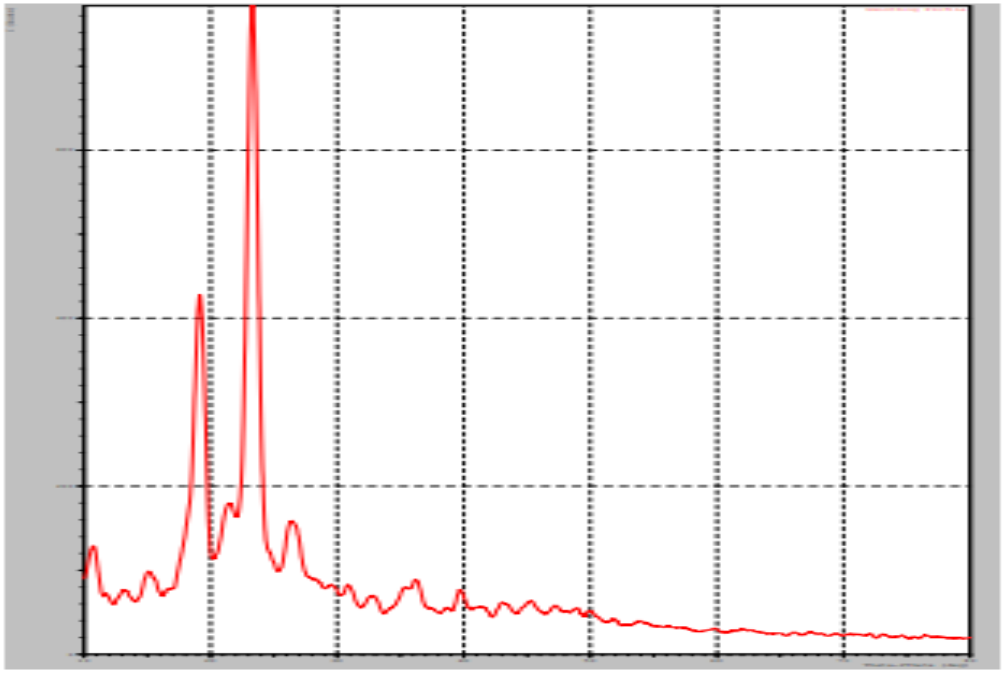

Fig 8.8: XRDIvosidenibI6 nanoparticles

Table 8.6:*In vitro* dissolution studies of I1-I9 nanoparticles formulations in percentage

Time (hour)	I1	I2	I3	I4	I5	I6	I7	I8	I9
0	0	0	0	0	0	0	0	0	0
1	31.94	23.19	16.37	12.54	16.71	26.23	20.72	15.41	10.38
2	38.63	30.82	26.24	26.41	33.82	32.90	28.14	22.34	15.29
4	46.17	48.90	32.99	35.05	40.19	37.44	35.76	28.92	20.71
6	52.89	56.17	38.50	41.60	46.53	46.15	45.10	32.76	26.92
8	68.16	67.36	45.17	50.35	55.75	53.20	50.28	40.63	30.49
10	75.24	73.51	56.11	58.12	62.89	57.38	61.19	53.21	42.58
12	86.71	76.52	67.06	69.28	77.93	65.02	64.98	60.34	47.26
18	97.25	85.10	75.53	75.46	85.42	70.11	70.75	67.27	52.15
24		98.17	83.42	86.65	90.82	86.97	78.15	75.34	64.87
48			92.78	90.87	92.36	99.13	90.37	86.27	80.62

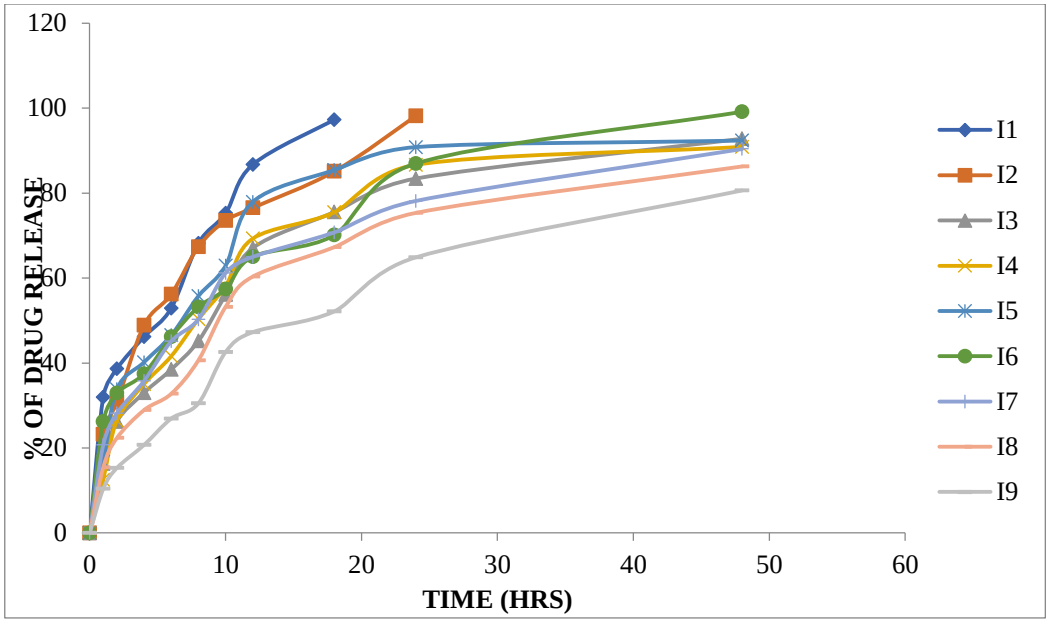

Fig 8.9:*In vitro* dissolution studies of I1-I9 nanoparticles formulations in percentage

In vitro drug release study of the selected nanoparticles (I1, I2, I3, I4, I5, I6, I7, I8 and I9) was carried out. The nanoparticles exhibited 48 hours sustained release pattern. 15.64 of the incorporated amounts of drugs were found to be released during the first 2 hours, followed by a slowed release of 99.13 % of the drug up to 48 hours. The Ivosidenib- loaded nanoparticles I6 showed a better release profile of 99.13% 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 I6 (Chitosan) is shown in Table and in following Figures.

Table 8.7: 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	Qt 1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
26.23	1	1.000	1.419	0.000	1.868	26.230	0.0381	-0.581	73.77	4.642	4.194	0.448
32.9	2	1.414	1.517	0.301	1.827	16.450	0.0304	-0.483	67.1	4.642	4.064	0.578
37.44	4	2.000	1.573	0.602	1.796	9.360	0.0267	-0.427	62.56	4.642	3.970	0.672
46.15	6	2.449	1.664	0.778	1.731	7.692	0.0217	-0.336	53.85	4.642	3.776	0.865
53.2	8	2.828	1.726	0.903	1.670	6.650	0.0188	-0.274	46.8	4.642	3.604	1.038
57.38	10	3.162	1.759	1.000	1.630	5.738	0.0174	-0.241	42.62	4.642	3.493	1.149
65.02	12	3.464	1.813	1.079	1.544	5.418	0.0154	-0.187	34.98	4.642	3.270	1.371
70.11	18	4.243	1.846	1.255	1.476	3.895	0.0143	-0.154	29.89	4.642	3.103	1.538
86.97	24	4.899	1.939	1.380	1.115	3.624	0.0115	-0.061	13.03	4.642	2.353	2.288
99.13	48	6.928	1.996	1.681	-0.060	2.065	0.0101	-0.004	0.87	4.642	0.955	3.687

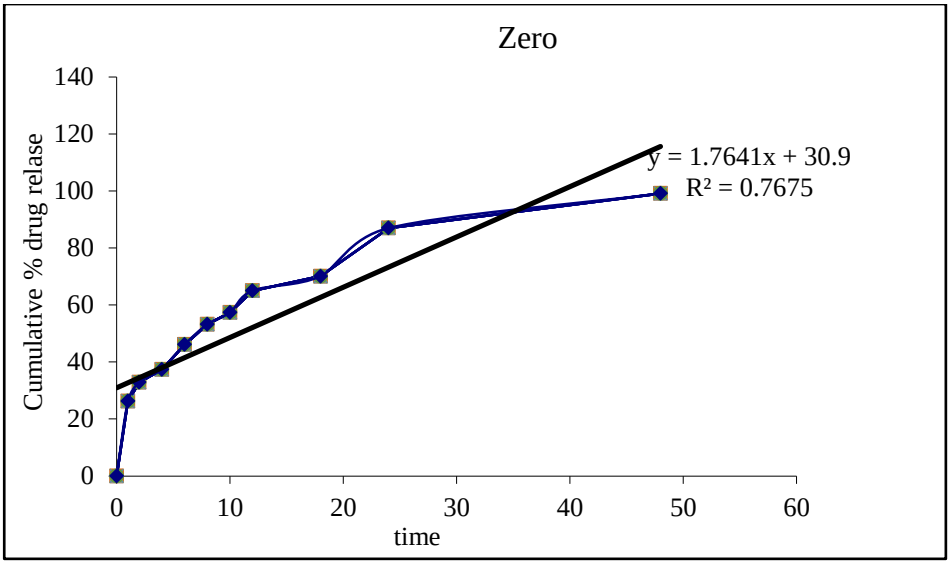

Fig 8.10: Zero order release kinetics

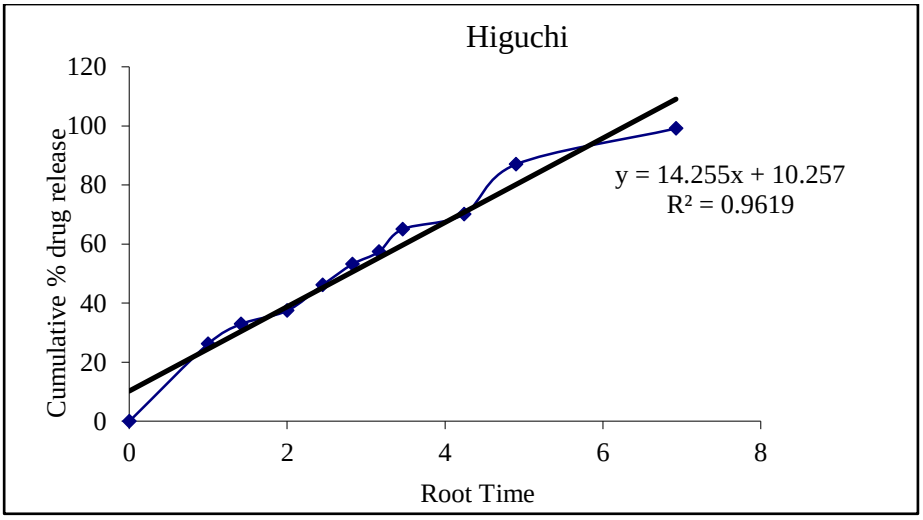

Fig 8.11: Higuchi release kinetics

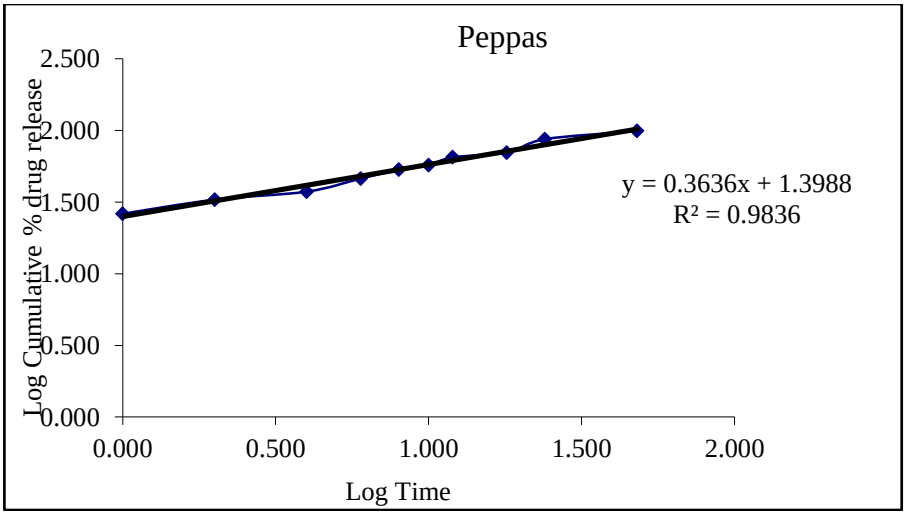

Fig 8.12: Peppas release kinetics

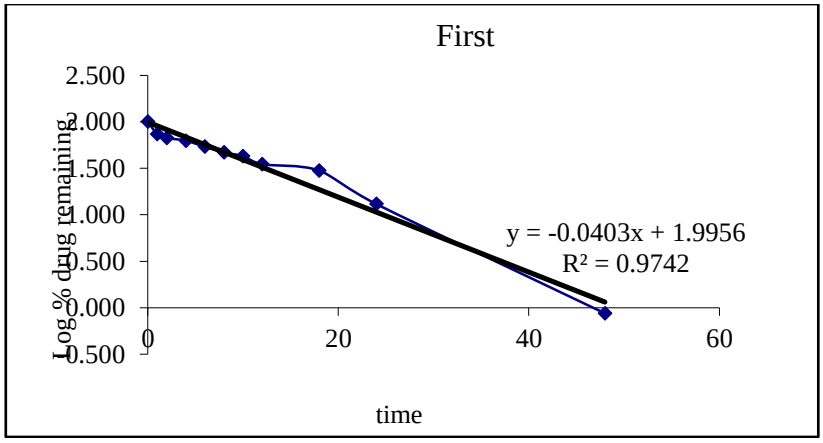

Fig 8.13: First order release kinetics

The prepared I6 optimized Chitosan 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 I6 optimized Chitosan a Nanoparticle was analyzed for the drug release mechanism. The best correlation coefficient value (0.9836) indicates the best release mechanism (Peppas release kinetics).

FTIR

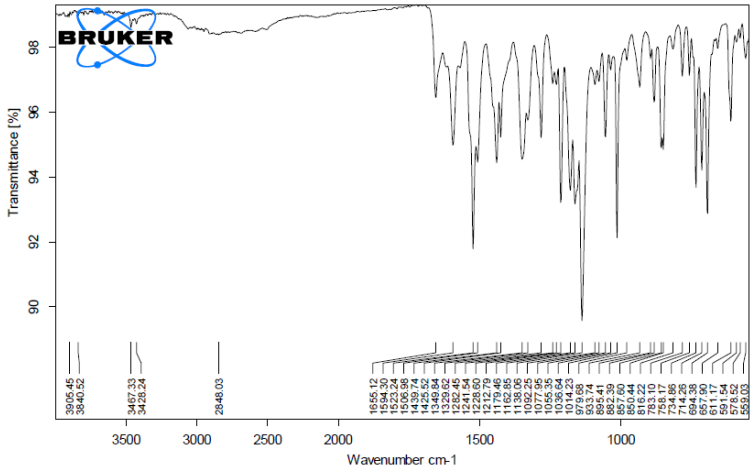

Fig 8.14: IvosidenibPure drug FTIR

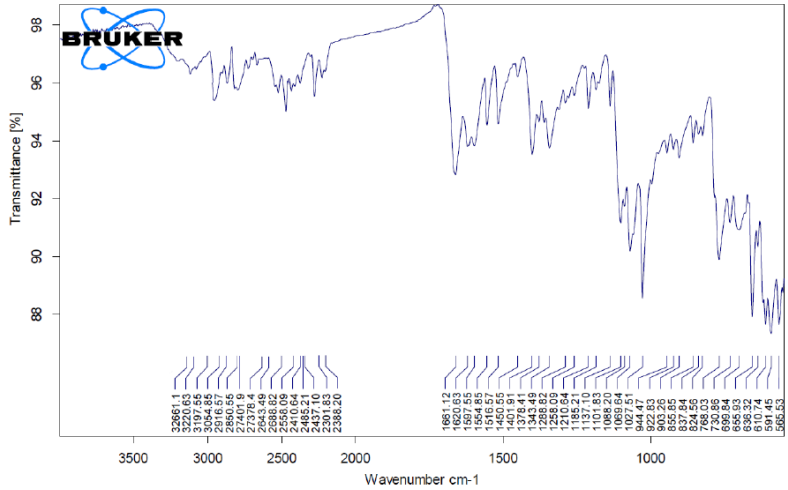

Fig 8.15: IvosidenibI6 optimized

Infrared studies were carried out to confirm the compatibility between the polymer, 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 nanoparticles. This indicated no interaction between the drug and other excipients.

CONCLUSION

Ivosidenib loaded polymeric nanoparticles were prepared by Emulsification sonication method. Drug polymer excipient comparability was confirmed by FT-IR and DSC investigations confirmed that there was no interaction between drug and polymers. The method resulted in consistent production of smaller size nanoparticles with narrow size distribution and good entrapment efficiency. From the results, formulation I6 containing Ivosidenib nanoparticles using combination of polymers evolved as the optimized formulation and it releases more than 99.13% drug in 48 hrs. The optimized formulation I6 can be considered as a promising sustained drug delivery system of Ivosidenib nanoparticles providing nearly Korsmeyer-peppas drug release over a period of 48 hrs. These results may prove to be beneficial for the prolonged utilization of the formulation as an acute myeloid leukemia and locally advanced or metastatic cholangiocarcinoma therapy. Thus, the polymeric nanoparticles may provide an effective drug delivery for poorly water-soluble lipophilic drugs.

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