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FORMULATION AND EVALUATION OF SONIDEGIB LOADED POLY ETHYL METHACRYLATE NANOPARTICLES TO TREATMENT CANCEROUS LESIONS

Praveen Kumar Dasari*, Kumar Raja Jayavarapu and Aguru Divya Sri

Mother Teresa Pharmacy College, Sathupally, Khammam, Telangana, India.

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Corresponding Author: Praveen Kumar Dasari

Address: Mother Teresa Pharmacy College, Sathupally, Khammam, Telangana, India.

ABSTRACT

The present research is about formulation and evaluation of Sonidegib loaded poly ethyl methacrylate nanoparticles (PEM-NPs) to improve its resistance towards pH and chemical conditions in exposed cancerous lesions. Based on design of experiment three batches F1, F2 and F3 Sonidegib loaded PEM-NPs prepared and characterized for Zeta potential (ZP), particle size (PS), polydispersity index (PDI) SEM, FTIR and PXRD studies. The PS of Sonidegib PEM NPs ranges between 191.5 ± 42.9 nm to 355 ± 39.7 nm. The particle size of the drug loaded NPs are considerably higher than unadorned nanoparticles. From in vitro release data a noteworthy improvement is observed in drug release of F3 when compared to pure Sonidegib. An improvement in drug release was observed in formulation F3 (95.878 %) than pure drug (2.86%) in in-vitro release studies. In-vivo pharmacokinetic studies were done to optimize Sonidegib PEM nanoparticles on rats, shown that C-max of the nanoparticles (98.43±4.21ng/ml) was significant ($p<0.05$), T-max of both nanoparticle formulation and pure drug suspension was 4.00±0.03 and 6.00±0.01h, respectively. The bioavailability was more than 5 folds increased in AUC0-∞ for nanoparticles formulation was higher (519.1±5.14 ng.h/ml) than the pure drug suspension formulation (93.7±6.22 ng.h/ml). These results marked that the proposed formulation was effective in improving the bioavailability of Sonidegib.

KEYWORDS: Sonidegib, poly ethyl methacrylate, nanoparticles, cancer lesions.

INTRODUCTION

Nanotechnology is exploitation of bio-material for producing novel nano-architecture with meticulous shape, size, form and properties for variable applications. Nanotechnology facilitates the drug distribution to specific cites aided by nanoparticles. The drug utilization and contrary effects are subsidiary by introducing the active agent in the targeted area. Targeted drug delivery by nano particles intends for reduction in adverse drug effects by decreasing consumption of drug in addition to decreased treatment expenses. Drug delivery emphasize on capitalizing the bioavailability of the drug that is achieved by Nano engineered devices (Jain et al., 2007; Singh et al., 2009) smaller in size, less interfering with easy implantation in human body in addition to faster working with improved sensitivity in comparison to typical drug delivery. Nanomedicine is an emerging interdisciplinary arena possessing potential applications warranting countless applications from therapeutic drug delivery to imaging in diagnostic fields. Bio-nanotechnology (BNT) possess greater potential to amend each critical component for clinical and scientific advances. (Wagner et al., 2006). Application of targeting concept to NPs has resulted in development of considerable interest of the same in biological field wherein targeting can be achieved in terms of active targeting and passive targeting. Various research has been done to achieve encapsulation of small molecular drugs hydrophilic and/or hydrophobic in nature, proteins and nucleic acid macromolecules into polymeric nanoparticles. Slow sustained drug release can be achieved by NP design at target sites. Polymeric nanocarriers can also provide many of the advantages of lipid systems and can be modified for target specificity. Liposomes, solid-lipid nanoparticles (SLNs), nanoemulsion, dendrimers and polymeric nanocarriers are some of the examples of widely used nanoparticulate drug delivery systems.

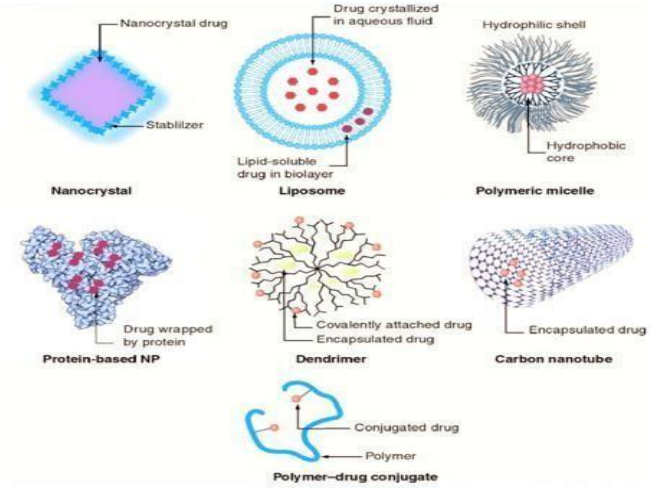

Figure 1: Types of nanotechnology-based drug carriers.

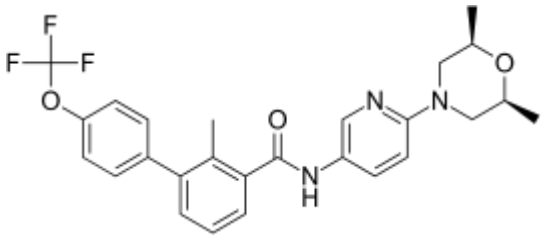

Figure 2: Molecular structure of Sonidegib.

Sonidegib is used in the treatment of advanced basal cell carcinoma post recovery from surgical cancer therapy. The total absorption of Sonidegib is fewer (roughly 6-7%). The low solubility of Sonidegib is due to low and dose-dependent absorption. Polymeric nanocarriers possessing hydrophobic shell dissolve the hydrophobic drugs for effective safe formulations. Amongst various hydrophobic polymers, the biocompatible polyester poly ethyl methacrylate is wildly used for drug delivery due to its resistance towards chemical hydrolysis, achiral and high permeability. The present research work is development and evaluation of Sonidegib loaded poly ethyl methacrylate nanoparticles to improve its resistance towards pH and chemical conditions in exposed cancerous lesions.

MATERIALS AND METHODS

Chemical analysis was performed using Fourier transformed infrared (FTIR) Spectrophotometer (Shimadzu FTIR 8400S, Japan). Powder X-ray diffraction patterns were carried out on X-ray diffractometer (Bruker D8 Advance). Thermal analysis was carried out using a Perkin Elmer DSC/7 differential scanning calorimeter (Perkin-Elmer, CT-USA). The morphology of the finely ground particles was observed under scanning electron microscopy (JOEL SEM, Model 6400F, JEOL, Tokyo, Japan). FTIR of Sonidegib recorded on 8400S Spectrophotometer over 4000 -400 cm-1 range with 4cm-1 resolution.

Characterization by DSC

5mg of Sonidegib taken into pierced DSC aluminium pan and analysed within 50-400ºC at a rate of 10º C/min increase recorded under nitrogen atmosphere.

Solubility study conducted at 28±1°C by dissolving 0.1g of Sonidegib in various solvents including H2O, phosphate buffers of various pH (7.4 and 6.8), acetate buffer (pH 4.5), 1/100N HCl (pH 2.0) and 1/10 N HCl (pH 1.0). All the test tubes stirred mechanically for 12h and allowed to settle down for 24 followed by centrifugation. The supernatant liquid from

each test tube is filtered, filtrates diluted to obtain 30 µg/ml and analysed at 276 nm spectroscopically.

UV Spectroscopy

About 1 µg/ml of Sonidegib prepared in various diluent systems is analysed for λmax. The sample was scanned A Shimadzu UV-2450 PC series spectrometer between 200 and 400 nm.

Preparation and characterization of Sonidegib PMDs

Polymerization

The polymerization carried out by mixing up of Sodium dodecyl sulfate (SDS), potassium peroxodisulfate (KPS) in propanol and water to reflex equipment. Contents heated to designated level and ethyl methacrylate (EMA) added drop wise over 90 minutes. On completion of addition the contents stirred at reaction temperature for prescribed aging time.

Characterization

Particle size measurement

The size of particle (PS) and the polydispersity (PDI) were measured using Light Scattering device (Brookhaven Instruments Corporation) at the angle of 90°, 20℃. The particle size obtained by this instrument is the hydrodynamic diameter (z-average diameter, effective diameter).

Preparation of Sonidegib loaded PEM NPs

The Sonidegib NP dispersion diluted to 10-folds out of which 2 ml is added dialysis membrane (12 kD) gradually until free drug observed membrane bag. The amount of free drug is estimated spectroscopically at 276 nm using equation.

$$Wt.\ of\ Sonidegib\ in\ NPs = Wt.\ of\ total\ Sonidegib\ added - Wt.\ of\ free\ Sonidegib$$

$$Loading\ efficiency\ (\%) = \frac{Wt.\ of\ Sonidegib\ in\ NPs\ (mg)}{Total\ wt.\ of\ NPs\ (mg)} \text{ X100}$$

$$Encapsulation\ Efficiency\ (\%) = \frac{Wt.\ of\ Sonidegib\ in\ NPs\ (mg)}{Wt.\ of total\ Sonidigib\ (mg)}$$

Characterization of Sonidegib loaded PEM nanoparticles

FTIR spectroscopy

FT-IR spectroscopy of Sonidegib and optimized formulations carried out on FTIR Spectrophotometer (Shimadzu FTIR 8400S, Japan).

X-Ray powder diffraction Studies (PXRD)

X-ray diffraction studies of Sonidegib and Sonidegib loaded PEM nanoparticles optimized formulations were recorded on X-ray diffractometer (Bruker D8 Advance) at a scan rate of 5 °/ min in the 2θ range from 2.5° to 60°.

Measurement of PS, PDI and Zeta potential (ZP) of SLN

The PS, PDI and ZP of Sonidegib loaded PEM NPs were measured by using a Zetasizer (Nano ZS90, Malvern, and Worcestershire, UK). From the prepared nano dispersion, 100 mL was diluted to 5mL with double distilled water to get optimum kilo counts per second (Kcps) of 50–200 for measurements.

Morphology by scanning electron microscopy (SEM)

The morphology of PEM nanoparticles was studied by Scanning Electron Microscope (SEM, Hitachi, Tokyo, Japan). The drug loaded PEM nanoparticles were suitably diluted with double distilled water (1 in 100) and a drop of nanoparticle formulation was placed on sample holder and air dried. Then the sample was observed at accelerating voltage of 15000 volts at various magnifications. Imaging was carried out in high vacuum.

In vitro drug release

The release was checked in falcon tubes where 1.5 mL of Sonidegib-PEM-NP dispersion was added to 1.5 mL of each of buffer (pH 7.4), buffered saline and bovine fetal serum in triplicate and incubated at 37°C up to 10 days. After periodic intervals, the samples were centrifuged at 3,000 rpm, the supernatant was discarded and the Sonidegib pellet was dissolved in 3 mL ethanol and analysed by UV visible absorption measurement at 276 nm.

Pharmacokinetic study of Sonidegib

Wistar rats of weight between 150-180 g chosen for the study that are maintained at temperature 25^0C, and Rh of 45% and 12 h under alternate cycles of light and dark, the animals are kept in room with 100 % fresh air, constant supply of power and water. The

animals fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee.

Rats were divided into two groups, at random. The rats were fasted for 24 hours prior to the experiments. After 4 hours of dosing, foods were reoffered. First group was administered with pure Sonidegib (Pure drug) and second group was administered Prepared Sonidegib nanoparticles by oral route at a dose of 3.125mg as per animal body weight. Then, 500 µL blood samples were collected from the femoral artery at certain times 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24h post dose and transferred into Eppendorf tubes containing heparin to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min to 10 minutes and stored frozen at −20°C until analysis.

Determination of Sonidegib in Rat plasma by HPLC method

25 mg Sonidegib hydrochloride was dissolved in 50 mL DMSO by using a shaker. 0.200 mL of this solution was added to 7.800 mL of DMSO in a polypropylene tube. A volume of 2.000 mL water was added and homogenized to obtain 200 µg/mL of stock solution. Aliqotes of 0-6 ng/ml prepared from stock solutions by diluting in water-DMSO (20:80, v/v). Determination of Sonidegib and internal standard Atorvastatin was carried out by using analytical column prepacked column Zorbax C-18, 5micrometer, column dimensions: 25cm x 4.6mm using mobile phase composed of acetonitrile, methanol and water at a ratio of 80:10:10v/v respectively. Sonidegib was detected at 254 nm with the flow rate of 1 ml/min in both mobile phase and plasma. Retention times Sonidegib and internal standard Atorvastatin was found to be 3.6 minutes and 2.5min.

RESULTS AND DICUSSION

FTIR Spectroscopy

Figure 3 depicts a strong bang within the region 2800-3200 cm-1 for the N-H stretching frequency confirming the structure of Sonidegib drug. The main characteristic infrared absorption bands were observed at 3180, 1685, 1610, 1487, 1487, 1065, 885, 863, 769 and 678 cm-1 authorizing the drug purity as per standards.

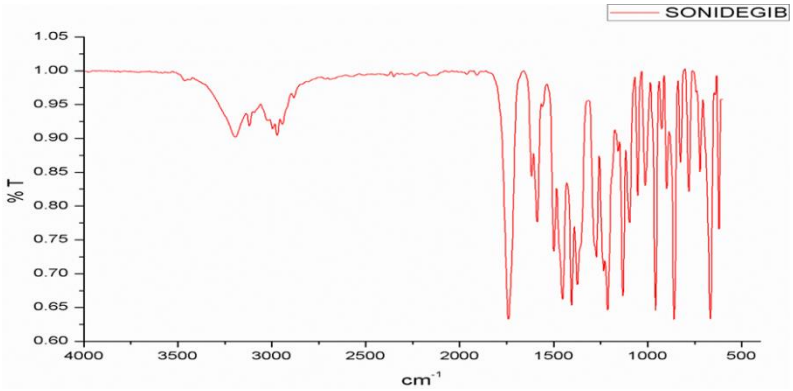

Figure 3: FTIR spectra of Sonidegib pure drug.

UV Spectra Analysis

The UV spectrum recorded in phosphate buffer diluent of pH 7.4 generated better output in comparison to other diluents. Sonidegib standard solution scanned within 200 nm to 400 nm against diluent as a blank. Sonidegib illustrates λmax 276 nm that agrees with the earlier reports.

Standard calibration graph of Sonidegib

The standard calibration curve of UV absorption vs. concentration of Sonidegib at 276 nm showed very good linearity characterized by good coefficient of correlation (R2= 0.9999) over the concentration range of 0-60 µg/ml. Thus it was found to obey Beer- Lambert's law over this range.

Table 1: Standard calibration graph of Sonidegib.

S. No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.208
3	20	0.341
4	30	0.444
5	40	0.645
6	50	0.754
7	60	0.893

Optimization and confirmation experiments

A numerical optimization technique using the desirability approach was employed to prepare Sonidegib nanoparticles with the desired responses. Constraints like maximizing the percent conversion and minimizing the particle size were set as goals to locate the optimum settings of independent variables. The optimized levels and predicted values of Y1 and Y2 are shown in Table 2. To verify these values, three batches of PEM nanoparticles were prepared

according to the predicted levels of A, B and C. Obtained Y1 and Y2 values were in a close agreement with the predicted values. This demonstrated the reliability of the optimization procedure in predicting the operating parameters for the preparation of PEM nanoparticles. All the three batches of obtained PEM nanoparticles were subjected to drug loading and further characterization.

Table 2: Optimized values obtained by the constraints applies on Y1 and Y2.

Independent Variable	Nominal Values	Predicted values		Observed values		
		Percent conversion (Y1)	Particle size (Y2)	Batch	Percent conversion (Y1)	Particle size (Y2)
Amount of surfactant (A)	1.4	97.09	199.11	1	96.82	204.2
				2	97.11	199.8
Reaction temperature (B)	85			3	96.23	208.3
Aging time (C)	60.5					

All the three batches of PEM nanoparticles were loaded with Sonidegib. The drug loaded PEM NPs analysed for FTIR and characterization studies.

Particle size (PS), PDI, ZP, EE and % drug loading

The PS of Sonidegib PEM ranges between 191.5 ± 42.9 nm to 355 ± 39.7 nm (Table 3). The PS of the formulations is higher than the plain nanoparticles. The PDI is between 0.454 to 0.626, representing a wide distribution range. The PMPs unveiled -ve surface charge on insertion of Sonidegib suggesting the alignment of drug within lipid matrix. The ZP value of -22.9 ± 2.48 mV to -24.7 ± 1.89 mV which >20 mV indicates stable formulation The -ve surface charge value of nano formulations enables the intestinal absorption through peer patches thus enhancing lymphatic absorption. The total EE value of the nano formulations lies between 68.46 ± 0.37 % to 70.24 ± 0.18 %. The % drug loading (DR) ranged between 20.62 ± 2.12 % to 21.24 ± 1.72.

Table 3: The mean particle size, PDI, zeta potential, entrapment efficiency and % drug loading of optimized Sonidegib PEM NPs.

Batch	MPS ± SD (nm)	PDI	ZP ± SD (mV)	% EE ± SD	% DR ± SD
F1	355 ± 39.7	0.626	-24.2 ± 1.68	70.24 ± 0.18	21.24 ± 1.72
F2	344.9 ± 41.6	0.475	-22.9 ± 2.48	68.46 ± 0.37	20.62 ± 2.12
F3	191.5 ± 42.9	0.454	-24.7 ± 1.89	69.72 ± 0.82	20.84 ± 0.94

Drug release study

The dissolution profiles of plain Sonidegib and Sonidegib nano formulation in GI medium. The drug release experiments showed a rapid and complete release of Sonidegib from nano formulation signifying improved release rates than pure drug. The release of pure Sonidegib is < 2% within 120 minutes, whereas the nano formulations exhibited faster release. An average 25–30 % Sonidegib was released within 60 minutes showing rapid burst release. The maximum release of Sonidegib after 120 minutes from F3 was 46.334%. After the 120 minutes the drug from nano formulation decreased due to dispersion of the Sonidegib captured within the nanoparticles.

Table 4: Drug Release data from Sonidegib and Sonidegib PEM NPs.

	% Cumulative drug release			
Time in hr	**Pure drug**	**F1**	**F2**	**F3**
0	0	0	0	0
0.25	0.07	7.822	8.125	7.123
0.5	0.112	15.863	15.898	14.1123
0.75	0.756	22.786	23.102	24.234
1	1.112	32.342	31.134	31.345
1.5	1.456	41.812	40.423	43.345
2	1.554	44.012	43.1123	46.334
3	1.781	54.345	52.356	58.346
4	1.881	63.545	61.456	64.472
6	2.212	74.585	71.112	73.112
8	2.322	79.678	78.457	80.113
12	2.389	88.791	86.732	85.146

HPLC analysis of Sonidegib and IS Atorvastatin was carried out by using analytical column prepacked column Zorbax C-18, 5micrometer, column dimensions: 25cm x 4.6mm with acetonitrile, carbinol and water at a ratio of 80:10:10v/v as mobile phase. Sonidegib was detected at254 nm at 1 ml/min flow rate. Retention times Sonidegib and internal standard Atorvastatin was found to be 3.6minutes and 2.5 min. Standard calibration curve plotted for varying concentrations of Sonidegib from 1-6ng/ml to check the linearity of developed method.

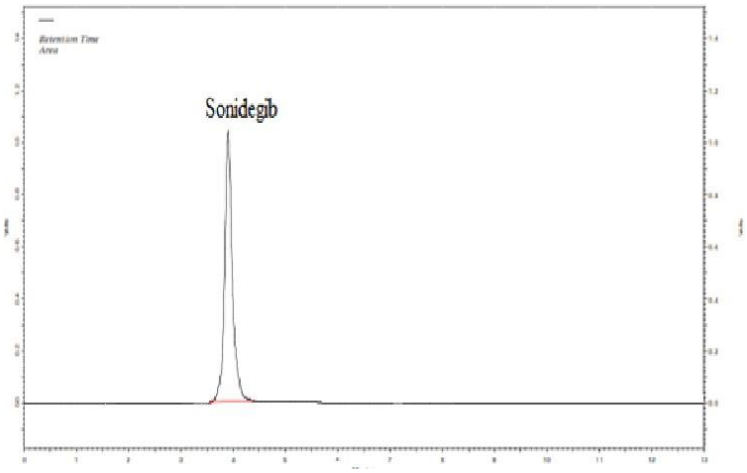

Figure 4: Standard HPLC Chromatogram of Sonidegib.

Pharmacokinetic parameters comparison for pure drug suspension and Sonidegib PEM NP (F3)

Figure 5 displays plasma concentration–time curve after a single dosage of Sonidegib PEM NP orally in comparison to pure Sonidegib suspension. At any point of time, the Sonidegib plasma conc. in animals administrated with nano formulation is advanced than those administrated with pure drug.

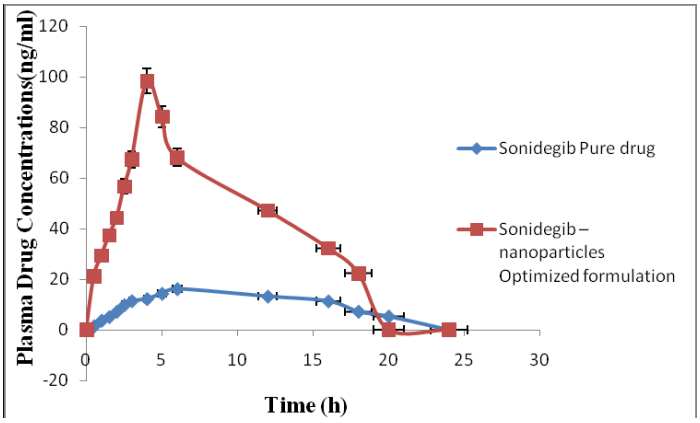

Figure 5: Plasma concentration profiles of Sonidegib PEM NP (F3) and pure drug.

C-max of the nanoparticles 98.43±4.21ng/ml was significant ($p<0.05$) than pure drug values of 16.15±1.56ng/ml. T-max of Sonidegib PEM NPs and pure Sonidegib were 4.00±0.03 and 6.00±0.01 h, respectively. The AUC0-∞ of Sonidegib PEM NP (519.1±5.14ng. h/ml) was greater than the pure drug formulation (93.7±6.22 ng.h/ml). Statistically, AUC0-t of the nanoparticles formulation was significantly higher ($p<0.05$) as compared to pure drug suspension formulation. Higher amount of drug concentration in blood indicated better

systemic absorption of Sonidegib from nanoparticles formulation as compared to the pure drug suspension formulation.

CONCLUSION

The current work is intended to develop and characterize Sonidegib loaded poly ethyl methacrylate nanoparticles (PEM-NPs) to improve its resistance towards pH and chemical conditions in exposed cancerous lesions. Based on design of experiment three batches F1, F2 and F3 Sonidegib loaded PEM-NPs prepared and characterized for Zeta potential (ZP), particle size (PS), polydispersity index (PDI) SEM, FTIR and PXRD studies. The PS of Sonidegib PEM NPs ranges between 191.5 ± 42.9 nm to 355 ± 39.7 nm. The particle size of the drug loaded NPs are considerably higher than unadorned nanoparticles. From in vitro release data a noteworthy improvement is observed in drug release of F3 when compared to pure Sonidegib. The in vitro dissolution data indicated an improvement in release of drug from formulation F3 (95.878 %) than pure drug (2.86%). The SEM studies indicated uniform stable distribution of drug in its nano formulations with spherical and porous structure. In vivo pharmacokinetic studies were conducted for optimized Sonidegib PEM nanoparticles on rats, C-max of the nanoparticles (98.43±4.21ng/ml) was significant ($p<0.05$). T-max of Sonidegib PEM NPs and pure Sonidegib suspension were 4.00±0.03 and 6.00±0.01h, respectively. AUC0-∞ for nanoparticles formulation was higher than Sonidegib suspension formulation, the bioavailability was more than 5 folds increased. These results marked that the proposed formulation was effective in improving the bioavailability of Sonidegib.

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