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POLYMERIC MICELLES: A NOVEL APPROACH FOR TARGETTING NON-SMALL CELL LUNG CANCER USING NINTEDANIB

SATHYAPRIYA O AND NITHYANANTH M*

Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore, Tamilnadu, India

***Corresponding Author: Mr. M. Nithyananth: E Mail: nithy.pharm@gmail.com**

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ABSTRACT

The present work was to explore the ability of amphiphilic block copolymer poloxamine (TETRONICS) to form polymeric micelles which acts as an effective drug delivery and targeting system for cancer therapy. The practical disadvantage of poloxamine due to its high CMC & cloud point is overcome by adding inorganic salt such as NaCl .The fabrication of class II drug Nintedanib into polymeric micelle was done by direct dissolution method. The formulation parameters were optimized using design expert software. Compatibility studies for drug and excipients were carried out by Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry the designed polymeric micelles were evaluated for its characteristic features like Cloud point, DLS, Entrapment efficiency and *In vitro* release studies. *In vitro* cytotoxic activity for its efficiency as a promising drug delivery system was established using MTT assay. The lyophilized form of micelles was examined for its surface morphology using scanning electron microscopy and phase contrast microscopy. The solubilization of anticancer drug nintedanib demonstrates improved controlled release kinetics and cytotoxicity. On the whole, modulation in micellar behaviour by NaCl opens enchanting possibility of using T1307 and T1107 micelles as nanoreservoirs for carrying poorly water soluble drugs.

Keywords: Polymeric micelles, amphiphilic block polymer, Tetronics, Design expert, non-small cell lung cancer

INTRODUCTION

Lung cancer is one of the most frequently diagnosed cancers and is the leading cause of cancer-related death worldwide. Every year, more than 1.6 million cancer-related deaths and more than 1.8 million newly diagnosed cancer cases are owing to lung cancer (13% of the total diagnosed cancer cases) **[1]**. A wide variety of lung cancers with different characteristics exist, from very slow-growing and surgically treatable SCLCs (15% of all new instances of lung cancer) to extremely hostile and widely metastatic NSCLCs (85%) **[2, 3]**. For many years, chemotherapy has been used to treat individuals with non-small cell lung cancer (NSCLC). Patients whose NSCLC can be removed by surgery will receive nintedanib treatment as adjuvant chemotherapy, those with advanced NSCLC acquire it as palliative therapy, and those with locally advanced NSCLC receive it as part of bi- or multimodality therapy **[4]**. One of the factors influencing a tumor's growth is angiogenesis, targeting this pathway is an appealing alternative. This approach has led to the development of numerous antiangiogenic medications, including bevacizumab, sorafenib, sunitinib, vandetanib, ramucirumab, motesanib, and many others. Nintedanib, a triple angiokinase inhibitor, was the most recent medication in this class used in treating non-small cell lung cancer (NSCLC) patients. This protein interferes with the pathways of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF), preventing the tumour from switching to typical escape mechanisms **[5]**. The drug should be administered parentally in order to target the tumour at inaccessible sites, and pharmaceutical drug carriers carrying the drug in plasma should have characteristics such as biodegradability, small particle size, high loading capacity, prolonged circulation, and accumulation in the necessary pathological site(s) in the body. One such approach is polymeric nanomicelles. Polymeric micelles are Nano scale drug delivery vehicles with a core-shell structure formed by the reversible self-assembly of amphiphilic block copolymers in aqueous solution which was triggered by thermodynamics **[6, 7]**. The hydrophilic block of the copolymer's corona serves as the outer shell of polymeric micelles, protecting the drug from the aqueous environment and stabilizing the polymeric micelles against identification in vivo by the reticuloendothelial system **[8]**. The hydrophobic portion of the block copolymer's inner core envelopes the medication that is poorly water-soluble. The core may occasionally consist of a water soluble polymer that has been chemically

conjugated with a water-insoluble drug and complexes with two oppositely charged polyion to form polyion complex (PIC) micelles **[9]**. Block copolymers can be found in solution as unimer, or single units, at low concentrations. While the solution approaches CMC, where the micellization or aggregation of unimer occurs, the entropy of the solution decreases as the concentration rises due to the unfavorable arrangement or ordering of solvent molecules. The CMC range of block copolymers is 10^{-7}–10^{-3}M in water and typical sizes of amphiphilic block copolymer micelles are 5-100 nm **[10]**. The recent development of less explored amphihilic block copolymers used for micelle formation includes Pluronics, Tetronics, and Soluplus etc. The X-shaped poloxamines (Tetronic®) have drawn interest recently because to the distinctive chemical architectures that amphiphilic copolymers can display. Four (PPO-PEO) arms (blocks) are present in poloxamines and are joined to an X-shaped structure with an ethylenediamine center **[11]**. The molecular weight, EO/PO ratio and hydrophilic-lipophilic balance (HLB) of poloxamine and the degree of protonation of the amine moieties strongly determine the self-associative behavior and temperature sensitiveness and, consequently, the performance as micellar carriers **[12]**. Similar to poloxamers, the poloxamines can create micellar and gel structures that can be applied to the pharmaceutical and biomedical industries as tissue scaffolds, ingredients in transdermal formulations, and in nanoparticle engineering. Tetronic can alter the bio distribution of drug-loaded nanoparticles that are delivered parentally or orally as well as providing steric stability **[13, 14]**.

MATERIALS AND METHOD:

Materials:

Tetronic 1107 (PRILL) & Tetronic1307 was obtained from BASF corporation, navi Mumbai and used as received. Nintedanib drug was received as a gift sample. Potassium di hydrogen orthophosphate was procured from Thermo Fischer scientific, Mumbai. Sodium hydroxide and sodium chloride was obtained from Nice chemicals, kochi.Purified water was obtained by reverse osmosis All other reagents were of analytical grade.

Methods:

Preparation of nintedanib loaded polymeric micelles

Polymeric micelles loaded with nintedanib were prepared using direct dissolution method. It commonly used for the hydrophobic copolymer such as poloxamers. The temperature is raised to form micelles through dehydration of core forming blocks. It involves the mixing of block copolymer and drug in an aqueous

solvent. It is commonly used for copolymer such as poloxamines and poloxamers **[15, 16]**. The temperature is increased to form micelles form through dehydration of core forming segments. In this experiment Tetronic 1107(1.875 g) and Tetronic 1307(0.625 g) were dissolved in aqueous solventwater. The electrolyte NaCl of two different concentrations of 0.05M and 2M was added to the polymer mixture to trigger the self-aggregation behaviour of block polymers into micelles. To this polymer–electrolyte mixture drug Nintedanib (6mg) was added to get loaded into the polymeric micelles. The mixture was left to stir in a magnetic stirrer for 2 hours with the temperature maintaining 45^0C to form drug loaded polymeric micelles.

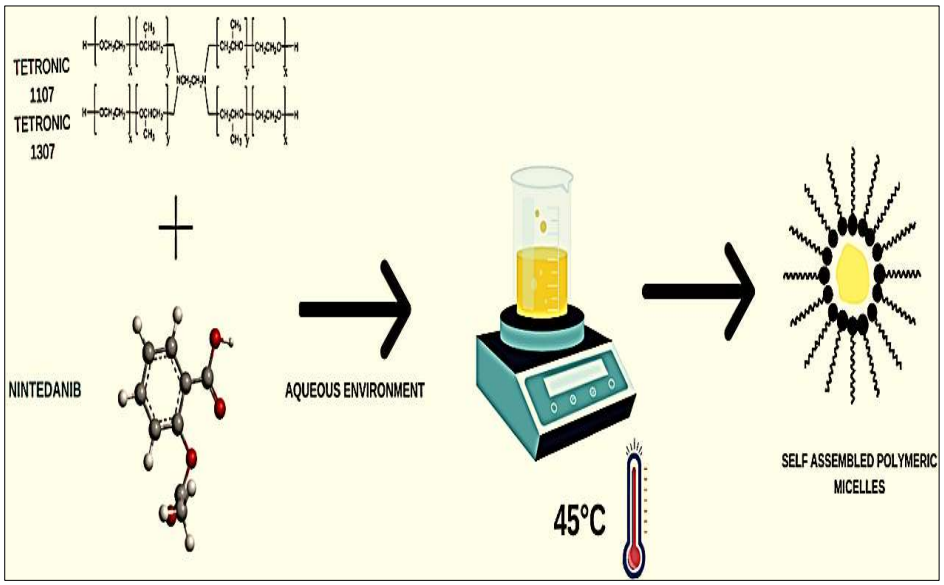

Figure 1: Preparation of Polymeric micelles

Optimization using full factorial design

NTB-loaded Tetronic micelles were formulated using a 2^3 full factorial design to study the impact of different nanomicellar variables using Design-Expert VR software (Version 11, Stat- Ease Inc., Minneapolis, MN). The independent variables fixed were the Sodium chloride concentration at two levels high (2M) and low (0.05 M), Tetronic concentration at two levels high (2%) and low (10%) and Tetronic ratios at two levels high (3:1) and low (1:1). The responses analyzed were Particle size (nm), Zeta potential (mV) and PDI. Design-Expert software was used to suggest the optimized formulation based on the criteria on minimum particle size, maximum Zeta potential, and decreased PDI. The optimum NTB-loaded micellar dispersion having the maximum desirability value which is approximately close to one was elected for further investigation. By comparing the

variance in the predicted R2 and adjusted R2 value, the precision of the model can be determined. If the difference between them within range of 0.2, they considered to be in a good agreement.

Functionalization of micelles with D-biotin:

Biotin coated polymeric micelles were prepared by the principle of electrostatic attraction. The final optimized formulation was slowly added to a magnetic stirrer containing biotin solution at a concentration of 0.5% w/v.The mixture was allowed for a overnight stirring at a stirring rate of 5,000 rpm.The surface coating of biotin was achieved by allowing the formulation to stirr under magnetic stirrer for overnight. The coating of micelles was confirmed by optical microscopy, SEM and Phase contrast microscopy.

Fourier transform infra-red (FTIR) measurement

FTIR spectra of Nintedanib, physical mixture of Nintedanib and Tetronic copolymer as well as freeze– dried biotin coated Nintedanib loaded Tetronic micelles were obtained with the potassium bromide (KBr) disc method (about 1:10 ratio of potassium bromide to sample) using Shimadzu Fourier Transform IR spectrometer (FTIR-8400S) **[17]**.

Thermal analysis

The thermal properties of the samples were characterized by a differential scanning calorimete (Mettler Toledo, DSC-3). Samples of Nintedanib, physical mixture of Nintedanib and Tetronic copolymer as well as the biotin coated Nintedanib - Tetronic micelles were enclosed in a pierced aluminium pan and heated in a nitrogen environment at a heating rate of 10º C / minute from 10 ºC to 300 ºC **[18]**.

Cloud point

The polymeric systems (10%) in different media (water, sodium chloride, buffer solutions) were sealed in glass vials and placed in an oil bath at room temperature to conduct the CP measurements. The temperature was then raised from 22°C (1°C/minute) to the point at which the system's optical appearance abruptly changed from clear to turbid. Analyses were performed twice. The CP measurement had a maximum deviation of 1°C **[19]**.

DLS

Micellar Particle size, Zeta potential and PDI of the prepared NTB-loaded Tetronic micelles were determined using a Zetasizer (Nano ZS-90, Malvern Instruments, UK) that examines the variation in light scattering due to particles Brownian movement. Each sample was measured by combining 1 mL of nanomicellar dispersion with 9 mL of distilled water and adding it to a quartz cuvette at 25 ± 0.5 ºC and 90 degree to the incident beam. Triplicates of each measurement were made (n=3) **[20]**.

Scanning electron microscopy (SEM)

SEM images were obtained in a ZEISS EVO-MA 10 microscope (ZEISS, Germany) having a tungsten filament operating at 20 kV. In order to be imaged using SEM, the specimen needs a conductive surface and has to be placed inside high vacuum. Samples were dried and mounted on a metal stub using a sticky carbon disc which increases conductivity. Silver-containing glue can additionally be applied for even more conductivity. Then the samples were viewed under high resolution microscope and the morphology of coated micellar samples can be captured **[21]**.

Invitro release studies:

The dialysis bag technique was used to measure the release of nintedanib from the synthesized polymeric Nano micelle in phosphate buffer PBS (pH 5.8) as the release medium. The cellulose dialysis bags (molecular weight cut off 12,000–14,000 Da) were soaked in the release media overnight prior to the release experiment. 2 ml of the NTB-loaded Tetronic micelle formulation (each 1 mL of the optimized formula contains 0.24 mg NTB) were added to the dialysis bag and tied at both ends. The dialysis bag was then placed in the beaker, containing 100 mL of PBS (pH 5.8) was and the mixture was shaken using a thermostatically controlled shaker at 37 ± 0.5 ºC. Samples were taken out at specific intervals for spectrophotometric analysis at λ max of 386 nm against a PBS (pH 5.8) as blank. The withdrawn samples volume was replaced by adding an equal volume of fresh PBS to the release medium **[22].**

***In-vitro* Cytotoxicity assay**

The viability was determined using a MTT assay. Briefly, the cells were cultured at MEM medium supplemented with fetal bovine serum 37 °C in a humidified atmosphere containing 5% CO2, dissociated with 0.25% trypsin in PBS (pH 7.4) and centrifuged at 1000 rpm for 7 min at room temperature. Then 30,000 to 40,000 cells were cultured in each well of 96-well plates and after 24 h time periods, to allow attachment of the cell to the wells, different concentrations of the materials were treated to the cells. In this context, different concentrations (10, 20, 30, 40….100 µg) Nintedanib loaded micelles were prepared with 1% DMSO and treated to the cells at different time periods. Besides, media containing 1% DMSO was used as negative control. The MTT assay was as follows: 20 µL of MTT solution (1 mg/mL) in PBS (pH 7.4) was added to each well. The incubation was continued for another 4 h and, then the solution was aspirated cautiously from each well. After treating the cells with Sorenson buffer, the optical density of each well was read using a micro plate reader (Multiskan MK3, Thermo Electron Corporation, USA) at a wavelength of 570 nm, and growth inhibition was calculated **[23]**.

Statistical data analysis

Values are represented as the mean ± SD. The statistical analysis was performed by a one-way ANOVA (Common significance levels are 0.10 (1 chance in 10), 0.05 (1 chance in 20), and 0.01 (1 chance in 100)) combined with the Tukey HSD test Comparison Test or t-test (5%significance level, P values smaller than 0.05 were considered statistically insignificant). The software was Graph Pad Prism version 5.00 for Windows.

RESULTS AND DISCUSSION:

Fourier transform infra-red (FTIR) analysis

Infra-red spectra of pure Nintedanib drug, drug-excipient mixture and final formulation were analyzed for its chemical adsorption of functional groups using Shimadzu Fourier Transform IR spectrometer (FTIR-8400S). IR analysis of physical mixture of drug and Tetronics shows the absorption peak at 3317.68 $^{cm-1}$ and 1251.84 cm^{-1} represents the presence of alkyne functional group with of C-H stretch and secondary alcohol group with C-O stretch respectively, in the structure of Tetronic polymers .The absorption peak at 1705.13 cm^{-1} represents the ether functional group with the stretching of C=O that confirms the presence of drug molecule in physical mixture. The broad absorption peaks at 1348.29 cm^{-1} represent the presence of alkane group with C-H bending that denotes coated biotin solution. The peaks at 3309.96 cm^{-1} represent the presence of Tetronic polymers which contains primary amide group with N-H stretch. Hence the drug and mixture was known to be compatible with each other and it can be further formulated. FT-IR spectra of final formulation retained the characteristic functional peaks of drug and excipients which ensures that there was no interaction between the drug and excipients **(Figure 2)**.

Thermal analysis

The compatibility study for drug and its excipients can be determined using Differential Scanning Calorimetry (Mettler Toledo, DSC-3). The Thermogram for samples were measured for its various characteristics features like purity, transition temperatures (melting, crystallization or curing) and examination of thermal history like exothermic and endothermic peaks. **Figure 3** depicts the temperature behaviour of the Nintedanib drug, physical mixture and biotin coated Tetronic micelle formulation. The temperature at which crystal water began to spill over was 135.3 °C, while the melting point of BIBF was 306.0 °C. The Nintedanib powder had endothermic peak at these two temperatures. The crystalline nature of the drug powder was represented by the sharp peaks which complies with the literature report **[24].** The physical mixture indicates temperature peak of Tetronic polymer at 55^0C and the endothermic peak

at 135^0C and 245^0C indicates the presence of drug, which showed that physical mixing was not enough to entrap the drug in polymer matrix. Likely the DSC spectrum for optimized formulation represent the presence of polymer endothermic peak at 55^0C and another peak was observed at 240^0C which denotes the melting point of biotin molecule that encapsulate drug molecule into it.

Optimization by factorial design expert

The formulation parameters were optimized using design expert software. The optimization was done by applying 2^3 factorial design which includes three main factors Sodium chloride concentration, polymer concentration and polymer ratio with low and high levels. The design results in 8 runs of different formulations. All these formulations were done in wet lab and the responses like particle size, zeta potential and PDI were feed back to the design and the desirability value was found. All the three responses (particle size, zeta potential and PDI) were tested for significance using ANOVA. The results were concluded to be significant by attaining p value which was less than 0.05.The desirability value was found to be 0.865 which was closer to 1. By this we can consider that the final optimized formulation was found to be **F7 (Table 2)**.

Cloud point

Uncharged water soluble polymers and non-ionic surfactants frequently exhibit the defining phenomena known as clouding. In this instance, phase separation results from dehydration in the hydrophilic portion of the copolymer micelle at high temperatures. The concentration, structure, and presence of additives all play a role in a copolymer's cloud value. A thermo responsive copolymer's CP is an important factor to take into account for drug delivery applications because copolymer solutions with CPs below 37 °C would precipitate when injected into a human body (whose physiological temperature is 37 °C), rendering their thermal targeting function ineffective **[25]**. In the case of EO-PO block copolymers, temperature, concentration, and hydrophobic interactions regulate the micelle formation. These copolymers' ability to self-assemble in aqueous conditions is primarily controlled by the different solubility's of their building elements. The solubility of both blocks decreases at increasing temperatures, which causes this aggregation process to occur. The PO and EO blocks exhibit good solubility at temperatures below CMT, allowing them to stay in the solution as unimer. The PO blocks, however, become insoluble when the temperature exceeds CMT and cause micellization. The cloud points for fixed concentration (1%) of Tetronics 1107 and 1307 were analyzed in various substances like water, buffers and in inorganic salts salt like NaCl. The cloud

point of both T1107 and T1307 exhibit high cloud point in water, whereas the CP decreases with increase in concentration of NaCl and pH. The results depicted in **Figure 4** were obtained by visual observation of the turbidity.

Dynamic light scattering

Size distribution of the assembled T1107 and T1307 copolymers was evaluated as a function of copolymer concentration, polymer ratio and salt concentration. At 250 C, 1 % Tetronic solutions in water only showed the presence of unimer or still small aggregates while typical micelles peaks along with the unimer peak were found for 2% and 10%(T1307+T1307) solution. Higher the salt concentration, better the micellization. The particle size for all the eight batches were in the range of (41.19-575.5 nm) From the design expert software the optimized formulation F7 shows the desired particle size of 112.1nm. The **polydispersity index (PDI)** of is a measurement of the particle size distribution's spread or homogeneity. The values of PDI <0.7, 0.1-0.7 and >0.7 are related to the highly mono-dispersed, moderately and highly poly-disperse distributions respectively. The PDI value for batches from F1-F8 lies in the range from 0.2 to 1. The PDI value for optimized formulation F7 was found to be 0.3 which denotes that the F7 was moderately monodisperse. This could be due to the presence of electrolyte in higher concentration 2M that promotes micellization and additional factor of optimized polymer concentration and ratio results the formulation with moderately monodisperse which confirms the absence of larger aggregates in the formulation. The **zeta potential** indicates electrostatic charges on the surfaces as well as the long term stability of nanoparticles in a formulation. To stabilize the nanoparticles electrostatically and sterically, a minimum zeta potential in the range of +30 mV to -30 mV is necessary. The zeta potential for the batches from F1-F8 was in range of - 3.9 to -16.5. The optimized batch F7 had a zeta potential in the range of -6.14 mV represents the existence of the optimum electrical barrier needed for formulation stability. The charge of the formulation were nearly found to be amphiphilic in nature, which was nor strongly positive neither strongly negative. The steric stability and reduced aggregation are attributed due to zeta potential **(Figure 5)**.

Scanning electron microscopy

The morphology of Nano micelle was investigated with the help of scanning electron microscopy by ZEISIS. Lyophilized micelle formulation of polymeric micelles is shown in **Figure 5**. The morphology of biotin coted polymeric micelles have been obtained as spherical in shape with nanometer ranges and

appearance of micelle as clusters may due to aggregation of nanoparticles during lyophilization **(Figure 6)**.

***In-vitro* drug release study.**

The in vitro release study of polymeric nanomicelle was studied using dialysis bag method. All the eight formulations were analyzed for release characteristics and the reports were tabulated below in **Table 2**. The release of NTB from micellar formulation under sink condition was investigated by dialysis method with Phosphate buffer pH 5.8 solutions as release medium. Once formulated into poloxamine micelles, the drug could be absorbed either in its free form or encapsulated in the carrier. In addition, a more sustained release would enable a much better fine tuning of the release profile. The release profile of any drug is highly influenced by the locus of the solubilized drug in the core-shell micelle. The final optimized formulation **F7** shows a maximum drug release of 77.5% in 6 hours. This may be due to the fact that the release pattern of drug from polymeric micelles from its hydrophobic core is in a **sustained manner** and it depends on **the length of the hydrophobic blocks and monomer species**. The formulations with sodium chloride concentration of 0.05 (low concentration) leads to lesser micellization that entrap less hydrophobic drug due to existence of more unimer where as high sodium chloride concentration leads to increased micellization with more drug entrapment promotes sustain release. Irrespective of polymer ratio and concentration sodium chloride concentration decides the drug release profile and particle size **(Figure 7)**.

***In-vitro* cytotoxic study**

The MTT assay was used to analyze the number of viable cells. Briefly, A549 cells were treated with a final formulation **F7** at a different concentration (0, 10, 20, 30…. 100 µg) and the MTT Reagents MTT Solution (1mg/ml), DMSO (100%), PBS (pH 7.2) was added to each well and incubated for 24 hours. The formazan generated from MTT was then dissolved in 150 µL of DMSO and thesupernatant was aspirated off. The plates were then analyzed using an enzyme-linked immunosorbent assay (ELISA) plate reader at a wavelength of 570 nm. Additional information of IC50 value was also identified **(Figure 8)**.

Y= mx+C,

From the above graph, Y=0.668x+21.83

M= 0.668; C= 21.83

IC 50= (50-C)/M;

IC 50= (50-21.83)/ 0.668

IC 50= 42.2µg

The given sample Polymeric Micelles showed Mild to Severe cytotoxicity to A549 cells after 24hrs. Then obtained IC50 value is **42.2µg.** Control solution polyurethane showed none Cytotoxicity as expected. The MTT assay was performed to calculate the

percentage of cytotoxicity and cell viability with respect to different concentration. This was mainly on account of the increased stability and solubility of the NTB inside the micelle core, and better uptake of NTB from NTB-loaded biotin coated micelles by the cells due to the overexpression of biotin receptors on A549 cytotoxic cell lines. Therefore, this formulation might serve as a potential nanocarrier to improve in vitro cytotoxicity of NTB **(Figure 9)**.

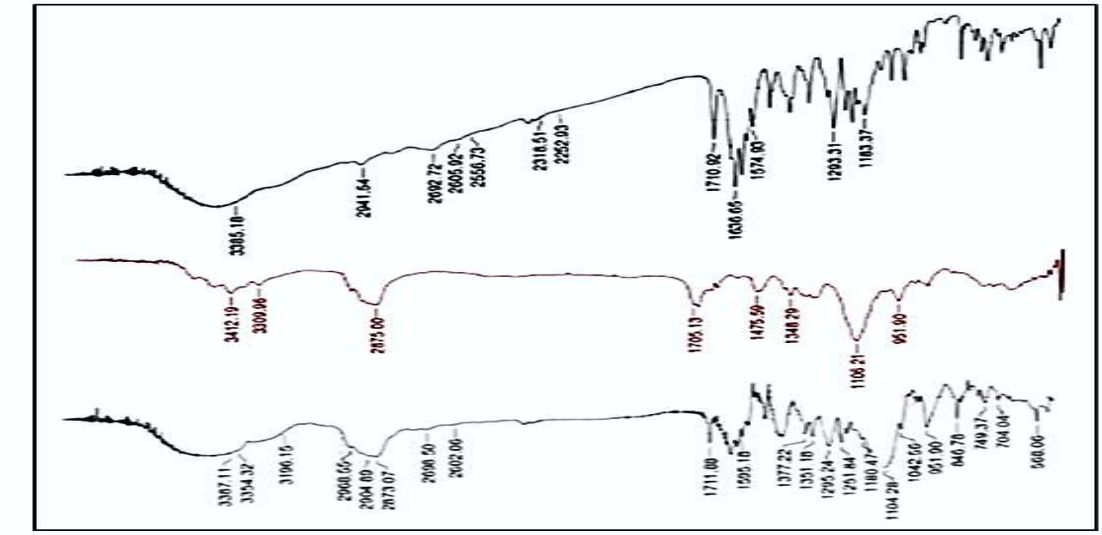

Figure 2: FT-**IR spectra of a) nintedanib b) Physical mixture c) Biotin coated NTB micelles**

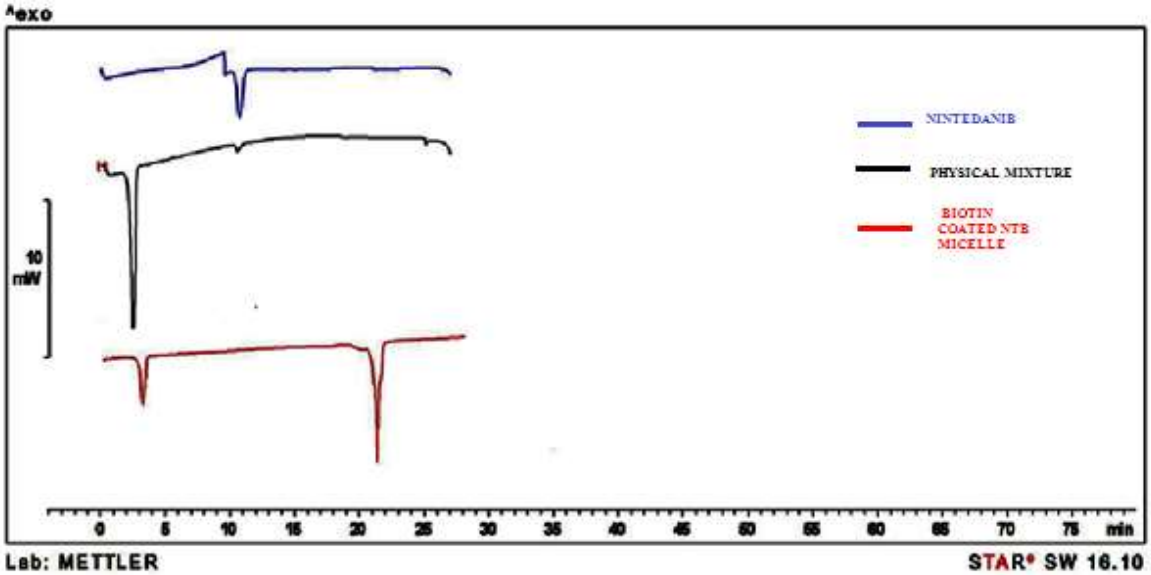

Figure 3: Thermogram for a) Nintedanib b) Physical mixture c) Biotin coated NTB micelles

Table 1: Constrains and goals fixed for optimization

S. No.	NAME	UPPER LIMIT	LOWER LIMIT	GOAL
1	Sodium chloride concentration	0.05	2	is in range
2	Polymer concentration	2	10	2
3	Polymer ratio	1	-1	3:1
4	Particle size	575.5	41.19	100 nm
5	Zeta potential	-3.9	-16.5	maximize
6	PDI	0.2	1	minimize

Table 2: Optimization of formulation parameters and its responses by factorial design

Batch Code	Factor 1 NaCl Concentration (M)	Factor 2 Polymer Concentration (%)	Factor 3 Polymer ratio	Response 1 Particle size (nm)	Response 2 Zeta potential (mV)	Response 3 PDI
F1	0.05	10	3:1	575.03±0.5	-14.5±0.4	0.9
F2	2	10	1:1	41.19 ±0.13	-3.86±0.5	0.3
F3	0.05	2	3:1	324.03±0.5	14.5±0.25	1
F4	2	10	3:1	167.1 ±0.79	8.36±0.25	0.7
F5	0.05	2	1:1	410.8±0.15	7.59±0.23	0.8
F6	0.05	10	1:1	534.40±0.51	-13.2±0.1	1
F7	2	2	3:1	112.03±0.8	6.46±0.56	0.3
F8	2	2	1:1	79.95± 0.1	-4.86±0.3	0.2

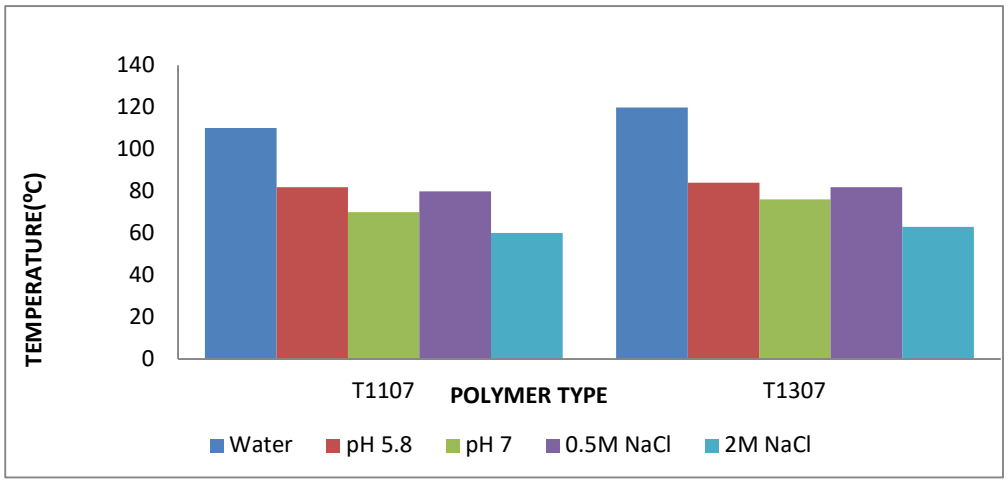

Figure 4: Cloud point for Tetronic in different media

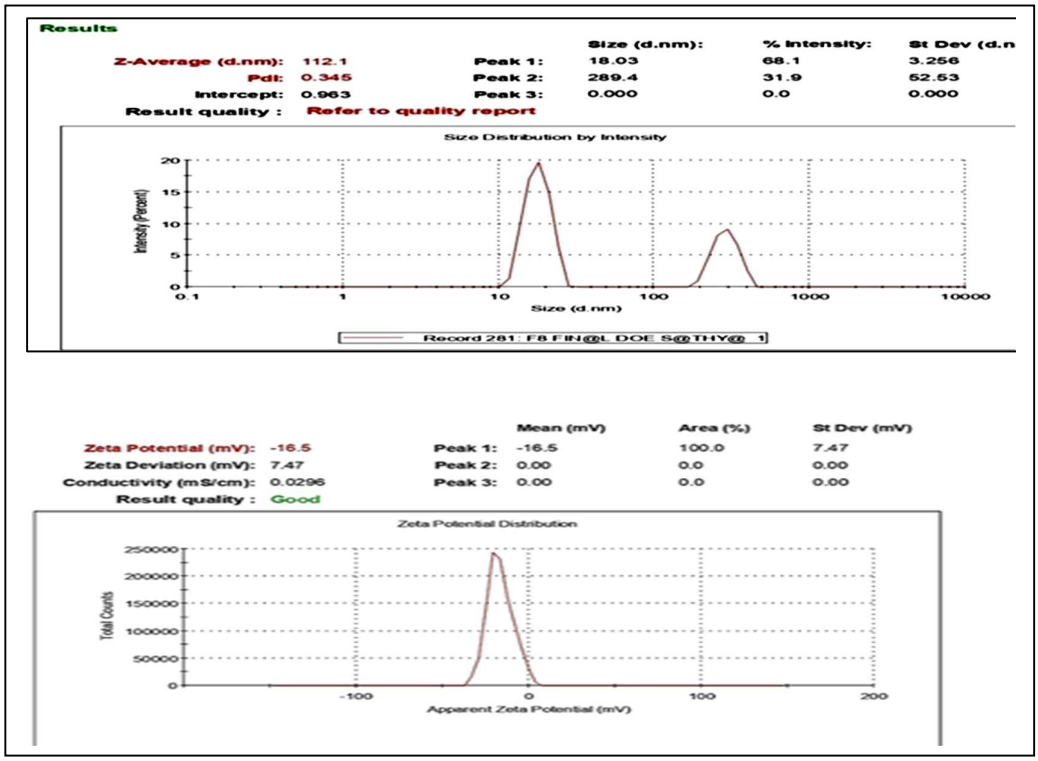

Figure 5: Size distribution and zeta potential for optimized formulation

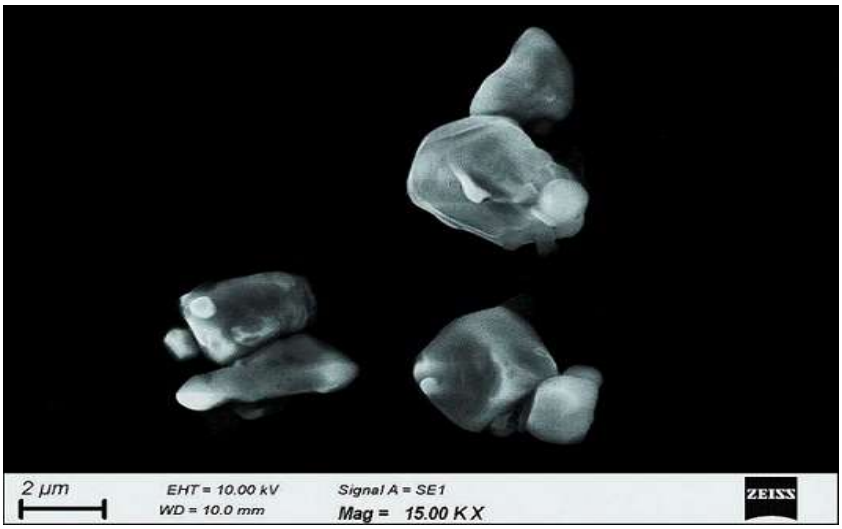

Figure 6: Morphology of biotin coated NTB coated Tetronic micelles

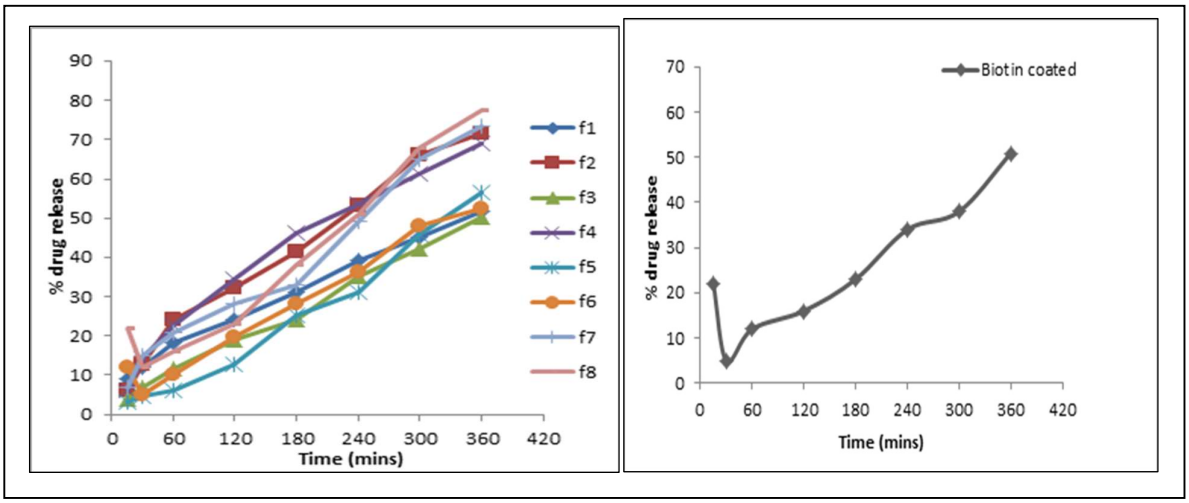

Figure 7: Release profile for formulation F1-F8 and biotin coated optimized formulation

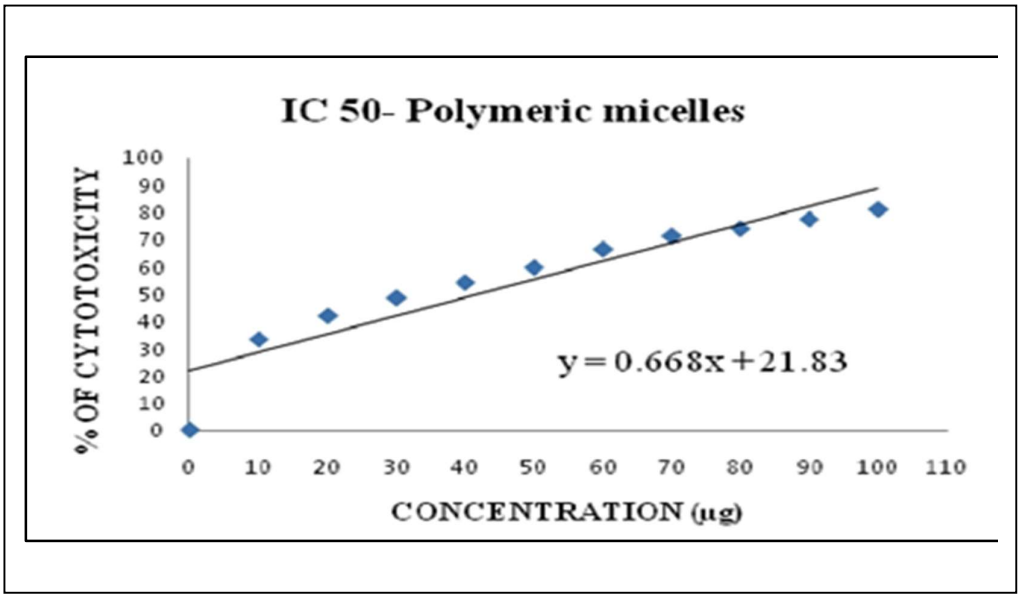

Figure 8: Determination of IC $_{50}$ Value for optimized formulation

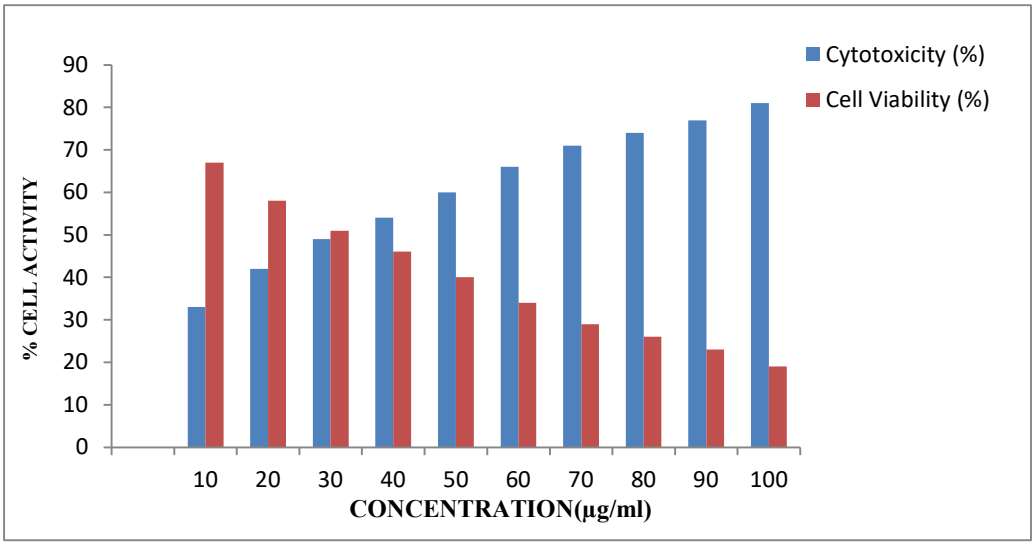

Figure 9: Cell viability and cell cytotoxicity

CONCLUSION

Polymeric micelles may offer improved stability, regulated drug release, and the potential to accept large drug payloads, among the many targeted drug delivery strategies employed in cancer therapy. Here the PM functionalized with D-BIOTIN may help in achieving longer circulation time and target cancer cells this could reducing the chemotherapy toxicities using novel Nano-carriers. In comparison with conventional chemotherapeutic treatments, Polymeric micelles loaded with Nintedanib may provide greater therapeutic impact with a lower dose. Thus it can be concluded that Nintedanib loaded nanomicelles can be formulated into a dosage form in future and will tested for preclinical studies which may possess a promising future in targeted drug delivery.

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