The Influence of polymers on Physicochemical Properties and *Invitro* Release of Erlotinib loaded nanomicelles: Development and characterization

Shruti Patel [*1], Asha Patel [2].

*[*1] Ph.D. Research Scholar, Department of Pharmaceutics, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India-391760*
[2] Associate Professor, Department of Pharmaceutics, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India-391760

Corresponding author: *Asha S. Patel, Department of pharmaceutics, Parul institute of pharmacy, Parul university, P.o.limda, ta: waghodia, Vadodara- 391760, Gujarat, India.*
E-mail:*patelasha1405@gmail.com*

Abstract

Erlotinib is epidermal growth factor receptor inhibitor (EGFR) used as first line therapy for treatment of non-small cell lung cancer. However, there are certain limitation which limits its use. To overcome that we have formulated erlotinib polymeric micelles. This study has investigated erlotinib loaded Pluronic F68, Pluronic F127 and TPGS polymeric micelles for micellar size, critical micelles concentration, entrapment efficiency, drug loading and In vitro drug release. Micellar size and PDI is characterise by dynamic light scattering. From results we investigated tocopherol polyethylene glycol has small micelles size in the range of 55nm-90nm compared to Pluronic F127 and Pluronic F68. Moreover,entrapment and drug loading were significantly increases to 69.2% by formulating TPGS micelles. In vitro drug release data predicts TPGS releases the drug in more sustain manner compared to Pluronic polymeric micelles. In nutshell, TPGS micelles would be platform delivery for targeting anticancer agents.

Key words: Targeted therapy, EGFR Inhibitor, Polymeric micelles, Lung Cancer.

Introduction

Erlotinib is approved targetedfirst line pharmacotherapy for treatment of lung cancer. Erlotinib is potential epidermal growth factor receptor (EGFR) inhibitor [1]. Cancer cells have an overexpressed protein receptors like epidermal growth factor which attach to the epidermal growth factor receptor and activated tyrosine kinase enzyme. Tyrosine kinase is responsible of triggering the chemical reaction that encourages cell division. Erlotinib binds with the epidermal growth factor receptor (EGFR) and thereby stop the binding of EGF to EGFR and activation of tyrosine kinase [2,3]. As a result, the cell will undergo apoptosis, which will inhibit further cell proliferation. However, erlotinib is a low-permeable, BCS class II medication with limited solubility. To increase solubility, a variety of methods have been used, including salt formation and development of nanostructures. However, at a pH of approximately 2, the equilibrium solubility of erlotinib hydrochloride salt is only about 0.4 mg/mL, which again paves the way to the development of nanostructure [4,5].

There are many attempts for development of erlotinib loaded nano formulation such as polymeric micelles, nanoparticle, microspheres. Nanocarriers helps to improve pharmacodynamic and pharmacokinetic profile of drug [6,7]. Drug molecule can encapsulate in polymer matrix by covalent bond and physical bond between drug and polymer. Desire encapsulations sustain the

drug release which can reduce drug toxicity and improves bioavailability [8]. Erlotinib encapsulation in hydrophobic core polymeric core material will help to improve solubility, entrapment and drug loading which is essential feature for bioavailability. Among the other nanocarriers, polymeric micelles is advantages for biocompatibility, reduced toxicity, sustain drug release and extensive retention and permeation at tumor site due to small size range [9].Polymeric micelles contain hydrophobic nonpolar core and polar outer corona which may assembled in aqueous media [10]. Hydrophobic drug get encapsulate in core structure and hydrophilic corona make micelles stable in aqueous environment [11].Hence polymeric micelles will be an efficient carrier for erlotinib to improve pharmacokinetic parameters and therapeutic efficiency [12].

In our study we have used three different polymer Pluronic F127, Pluronic F68, TPGS to encapsulate the drug in polymeric small vesicles. Amphiphilic polymers have low motility and slower diffusion rate. Moreover, nonionic surfactant has low CMC value compared to other low molecular weight surfactant. Pluronic F127, Pluronic F68, TPGS are widely used as amphiphilic carrier for sustain the release of drug.Pluronic polymer consist of two block polyethylene oxide (PEO) and polypropylene oxide (PPO) arranged in A-B-A manner [13]. Pluronic F127 and Pluronic 68 consist of PEO_X-PPO_Y-PEO_X molecular ratios of 100:65:100 and 76:29:76, respectively [8]. Pluronic block polymers are widely employed for the development of micelles since they are quickly eliminated from the body and provide minimal danger of toxicity. Pluronic F 127 is reported for enhancement of bioavailability for berberine [14], curcumin [9] and bufalin [15].MoreoverPluronic is reported to use for treatment of drug resistant cancer [16]. The United State F and D Administration has also authorized TPGS, a derivative of tocopherol and polyethylene glycol 1000, for use in humans as a surfactant, permeation enhancer [17,18]. Through micellar solubilization, it has been discovered that TPGS can improve the aqueous solubility of a variety of hydrophobic drugs including estradiol and docetaxel [19,20].

This study aim to develop and evaluate erlotinib loadedPluronic F 127, Pluronic F68 and TPGS polymeric micelles for physicochemical properties, entrapment efficiency, *invitro* drug release.The presence of various polar and nonpolar portion in the copolymer is the one factor that influences the functionality of polymeric micelles which collectively affect hydrophobic drug's potency, durability, absorption, and in vitro drug release study [8].Pluronic F127 and F68 and TPGS encapsulated erlotinib polymeric micelles has never been reported. In this research work we have developed erlotinib loaded polymeric micelles and characterized for micellar size, zeta potential, PDI, entrapment efficiency and drug release.

Materials and Methods

Material: Erlotinib was provided as gift sample from BDR Pharmaceuticals International Pvt. Ltd, Mumbai, India. Pluronic F-127 and Pluronic F 68 was purchased from Sigma Aldrich Chemical Pvt. Ltd (India). DL-α-Tocopherol methoxy polyethylene glycol succinate (TPGS)was purchased from Sigma Aldrich Chemical Pvt. Ltd (India). Ethanol (pharmaceutical grade) was procured from Sigma-Aldrich, Chemical Pvt. Ltd India. Acetonitrile, Methanol, purified water, orthophosphoric acid were purchased from Sigma-Aldrich Chemical Pvt. Ltd (India). All chemicals were in analytical grade.

Method for preparation drug loaded polymeric micelles: The polymeric micelles was prepared by solvent evaporation method(21,22). The polymers Pluronic F 127, Pluronic F68 and TPGS were taken with drug in the ratio of 1:1 to 1:5. Composition of each batch is shown in Table I. Erlotinib is hydrophobic molecule so common organic solvent ethanol was

selected to dissolve drug and polymers. The individual polymer and erlotinib at their required concentration was dissolve in 5 ml methanol. The organic phase added in 10 ml aqueous phase drop by drop under continuous magnetic stirring. The organic phase is evaporated by continuous stirring for 3 hours at 40°C. The final volume 10 ml was adjusted by adding required amount of deionized water. The final formulation was centrifuged at 4500 rpm and eliminate unentrapped drug aggregate and the supernatant layer was recovered for additional characterization.

Table 1: Compositions of erlotinib loaded polymeric micelles.

Drug : Polymer	Amount of drug erlotinib (mg)	Amount of polymers (Pluronic F127, Pluronic F 68, TPGA) (mg)	Organic solvent volume (ml)	Deionized water volume (ml)
1:1	25	25	5	10
1:2	25	50	5	10
1:3	25	75	5	10
1:4	25	100	5	10
1:5	25	125	5	10

HPLC analysis [23]: High performance liquid chromatography was used to measure concentration of erlotinib. For HPLC analysis C18 column shim-pack VP ODS (250 mm × 4.6 mm, 5 µm) was chosen, and analysis was done at a room temperature. Sampling volume was 20µland flow rate was 1 ml/min. Erlotinib hydrochloride was detected at lambda max of 332 nm. For efficient analysis the mobile phase was selected in the ratio of organic phase to buffer solution. The organic solution was mixture of 15% (v/v) methanol, 45% (v/v) acetonitrile with the phosphate buffer 40% (v/v) and pH adjusted to 4.5 with orthophosphoric acid.

To prepare the stock solution of erlotinib, 10 mg of the drug was dissolved in 50 ml of potassium phosphate buffer, and pH was adjusted to 7.4 with 0.2 M of sodium hydroxide. This produced a solution with a concentration of 200 µg/ml of the drug. Working standard solution was prepared from original stock solution in the range of 0.3, 0.62, 1.25, 2.5, 5, 10 and 20 µg/ml for further analysis.

Critical Micelles concentration [24]: The dynamic light scatter technique was used to estimate the critical micelles concentration of micelles using Zetasizer. Concentration range from 0.01mM to 1mM were analyzed for percentage light intensity at a scattering angle of 90° for each sample at 25°C. The light intensity and the sample's molar concentration were plotted on a graph. The CMC was calculated from the point where the slope of the intensity increased dramatically, indicating micelle production.

Size determination: Dynamic light scattering was used to determine the uniform size distribution of micelles.DLS measurements were carried out in all cases utilizing a photon correlation spectrometer in Zetasizer NanoZS, Malvern Instruments Ltd., UK, which can detect particle sizes between 0.6 nm and 6 µm at a constant scattering angle [25]. The measurements were performed in triplicate at 25°C. The electrophoretic mobility was translated into the zeta potential using a clear disposable zeta cell with a filed strength of 20 V/cm and aqueous medium as a dispersion media.

Encapsulation Efficiency and drug loading [26,27]: Entrapment efficiency and drug loading capacity were measured using the validated HPLC method at absorption maxima of 332nm. To maintain the uniformity, the Erlotinib loaded micelles were first subjected to membrane filtration through 0.22-micron syringe filter, followed by dilution with methanol with culmination

in drug release.It is noteworthy to sonicate the micelles for 15 minutes after dilution to obtain the micellar fraction.

$$EE\% = \frac{Weightofencapsulateddr}{Weightoffeedingdrug} \times 100\% [1]$$

$$DL\% = \frac{Weightofencapsulateddrug}{Weightofpolym} \times 100 \quad [2]$$

***In vitro* release [28]:**The highest entrapped batches of all polymers was evaluated for *in-vitro* release studies by HPLC analysis using Dialysis bag methodology. For the sample preparation, equivalent amount of lyophilized powder of polymeric micelles was dispersed in 10 ml of phosphate buffer (pH 7.4 and pH 5.5), in order to determine the efficiency at both the physiological and site-specific pH conditions with timely maintenance of sink conditions. The diffusion cell was further kept inside the incubator shaker at 37.0±0.5°C under gentle agitation at 100 rpm. The experiment was carried out in triplicate to check reproducibility. The drug release kinetics was determined for zero order, first order, Higuchi model and Kors-Peppas model.

Result and Discussion

Critical micelles concentration: The CMC value get affected by aggregation number, temperature, concentration and shape of micelles [29].Pluronic F 127, Pluronic F 68and TPGS sample solutions ranging from 0.01mM to 1 mM were prepared at 25°C and light intensity was measured. Below CMC value light intensity of each solution is constant. As CMC reached drastically light intensity increases due to presence of micelles. Figure 1(A) demonstrates Pluronic F 127 increases light intensity starting at 0.03 mM and TPGS at 0.02 mM, which is close to the reported value of 0.02 mM for both polymers [30.31].Figure 1(B)shows Pluronic F 68 has CMC value of 0.4 mM, which is in good agreement with published values ranging from 0.4 to 1 mM(32).Due to fewer hydrophobic units, the CMC value of F 68 is higher than the values for F 127 and TPGS.Pluronic F68, F127, and TPGS have reported HLB values of 29,22, and 13.2 respectively [33].The higher the HLB value, lower the hydrophobicity, and higher the CMC value.

Particle size: The micellar size and PDI value of Pluronic F68 micelles were in the range of 143.9nm-171nm and 0.026-0.272 respectively. Mean while Pluronic F 127 micellar size and PDI range from 139nm-113.6nm and 0.055-0.46 respectively as shown in figure 2. Pluronic F 68 has shorter chain length compared to Pluronic F 127. Pluronic F 68 has PPO/PEO ratio 0.24 and Pluronic F127 has PPO/PEO ratio 0.43 [34]. More hydrophobic unit reduces the micellar size of Pluronic F127 compared to Pluronic F68. Figure 2 demonstrates micellar size of erlotinib loaded polymeric micelles of Pluronic F68, Pluronic F127 and TPGS.

The micellar size and PDI of Tocopheryl polyethylene glycol succinate (TPGS) were 90.69nm-55.83nm and 0.11- 0.288 respectively. There is great difference between TPGS and Pluronic polymers micelles. One of the reason attributed to HLB value of polymers. Tocopheryl polyethylene glycol succinate (TPGS) has more hydrophobicity compared to Pluronic block polymer resulted into more compact structure. In addition to that TPGS has low CMC value at low concentration micelles will form.

As same mass ratio, increasing in the drug with polymer significantly gradually decreasing micellar size and change in PDI. These can be attributed to increasing in polymer concentration may enhance interaction between hydrophobic unit resulted in denser structure [35]. As concentration increases above CMC value existence of micelles, unimers and large aggregates is also increases resulted in variation to PDI(36).The observed zeta potential of micelles of all polymers with 1:5 ration of Pluronic F 68, Pluronic F 127 and TPGS are-0.84,-1.74mV

and -9.26mV. Due to the presence of the PEG and PEO chains, which arranged at outer layer and prevented them from aggregating even though the potential values were weakly negative, the micelles stabilization occurred primarily by steric hindrance rather than electrostatic repulsion.In addition to that the size between 10 and 100 nm is thought to be the best for avoiding the first-pass elimination and entering the tumor by penetrating the leaky vasculature. It will also be effective to reach the cancer cells because of its small size.

Surface morphology is observed by inverted microscope shown in figure 3. Polymeric micelles of Pluronic F68, Pluronic F127 and TPGS was found to be spherical in shape. When polymer get dissolves in water hydrophobic block will try to migrate in micellar core and hydrophilic portion will bent in loop structure. This resulted into flower like spherical structure.Due to high hydrophilic corona micelles gets highly repulsed and tend to behave like individual structure and non-aggregated.

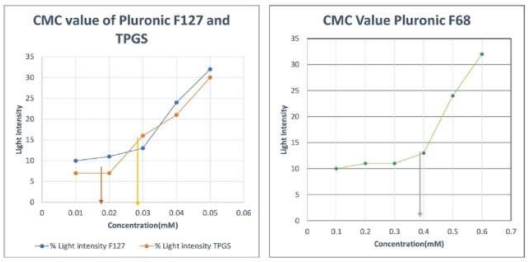

Figure 1(A) CMC value of Pluronic F127 and TPGS (B) CMC Value of Pluronic F 58

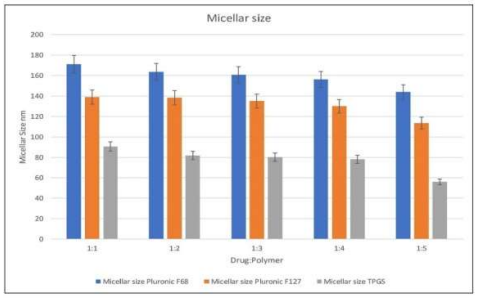

Figure 3 Micellar size of erlotinib loaded pluronic F68, pluronic F127 and TPGS

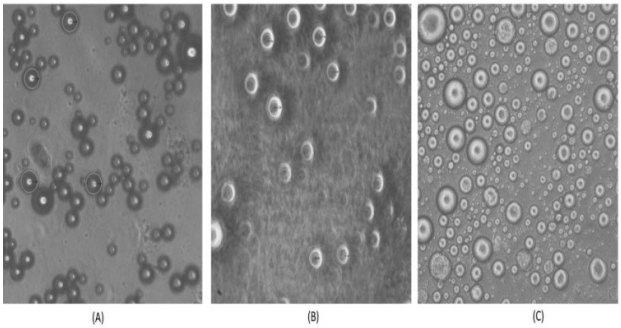

Figure 3 Surface morphology of (A) Pluronic F68 micelles (B) Pluronic F127 (C) TPGS micelles

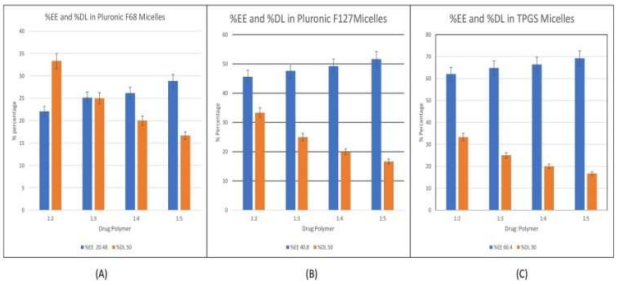

Figure 4 % Entrapment efficiency and Drug loading of (A) Pluronic F68 micelles (B) Pluronic F127 (C) TPGS micelles

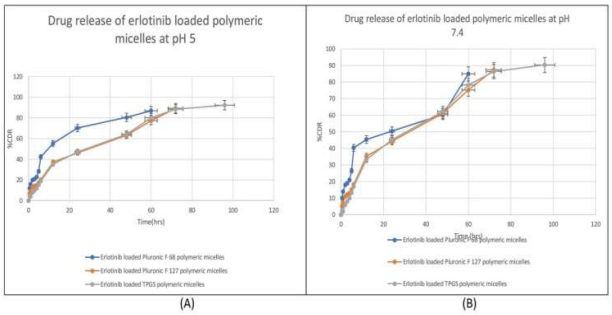

Figure 5 % In Vitro drug release polymeric micelles at (A) pH 7.4 (B) pH 5

Entrapment efficiency and drug loading

Effect of polymer type: The comparative % Entrapment efficiency and drug loading is shown in figure5. TPGS has high %DL and %EE (69.2%) compared to Pluronic F 127(51.6%) and Pluronic F 68(28.88%) at ratio 1:5 of drug to polymer. In comparison of Pluronic F 68 and Pluronic F 127, Pluronic F 127 has highest %EE and %DL to 51.6% and 16.66 %. This is due to low HLB value of Pluronic F 127 (22) compared to Pluronic F 68(29). However, In comparison to TPGS, Pluronic block co polymer has not vast difference. TPGS has lowest HLB value of 13.2 makes more stronger hydrophobic core structure with more improved hydrophobic

interaction with erlotinib. Collectively low CMC value and strong hydrophobic core makes TPGS more efficient polymer carrier compared to Pluronic F 127 and Pluronic F 68.

Effect of polymer concentration: In comparison to mixed micelles single polymeric micelles has not much impact of concentration on % entrapment efficiency and % drug loading. Pluronic F 68 polymeric micelles ranging ratio from 1:1 to 1:5 (Drug: polymer) results in entrapment of drug from 20.48% to 28:88%. Pluronic F 127 polymeric micelles entrap the drug 45.65% to 51.6% by increasing the ratio of 1:1 to 1:5. Furthermore TPGS gives best entrapment in the range of 60.4% to 69.2% by varying the ratio of drug to polymer from 1:1 to 1:5. CMC value of each polymers suggests that at high concentration a greater number of micelles are available to entrap the erlotinib. Drug-loading capacity and encapsulation is depending on factor like structure of molecule forms inner core, hydrophobic chain length and total mass ratio of polymer taken with the drug. As discussed previously Pluronic F 127 has PPO molecule number so more hydrophobic unit responsible drug interaction [34]. The hydrophobic drug and the micelle core mostly interact at the hydrophobic -CH3 group in the PO chain of Pluronic block copolymers [37].

In vitro drug release: A dialysis method was used to study *invitro* drug release of high entrapped batches for all the three Pluronic F127, Pluronic F68 and TPGS polymeric micelles in 7.4 phosphate buffer. The interaction of hydrophobic unit with drug like vender vales forces, covalent bond and physical entrapment is mainly responsible for the drug release kinetics. The slower and longer-lasting release of erlotinib from TPGS, Pluronic F127 micellar nanocarriers than from Pluronic F68 can be attributed to the higher interaction between erlotinib molecules in Pluronic F127 micelles. AT the initial 4 hours F 68 releases 21%, Pluronic F 127 releases 13% and TPGS releases 10% of erlotinib. Mainly the drug can be entrapped in polymer by three different location like inner core, core-corona interaction, and outer shell wall. The drug deposited on outer cell wall immediately release into bulk solution while drug located in inner core have long diffusion length or pathway. The burst release is triggered by the drug located at the core–corona interface or at corona. AT the initial 4 hours F 68 releases 21%, Pluronic F 127 releases 13% and TPGS releases 10% of erlotinib. Initial burst release from Pluronic F68 is attributed to more diffusion of drug from hydrophilic matrix. After 4 hours TPGS and Pluronic sustain the erlotinib releases up to 96 hrs and 72hrs respectively. At 96hrs TPGS drug release was found 88.09% while Pluronic F127 releases 87.33% drug in 72 hrs. Pluronic F 68 releases 86.45% erlotinib in 60 hrs. Because effective chemotherapy necessitates that the anti-cancer drug concentration in the blood be maintained between the minimum effective therapeutic level and the maximum tolerable level for longer periods of time, Pluronic F127 and TPGS polymeric micelles are well suitable carrier for erlotinib.

In vitro drug release was also per form at pH 5 to mimic the environment at cancer site. *In vitro* drug release of Pluronic F 68 polymeric micelles was found 86.91% at 60 hrs. Pluronic F 127 and TPGS polymeric micelles drug release was found 89.33% at 72 hrs and 92.3% at 96 hrs respectively. One of reason is erlotinib has pH dependent solubility. However, there are very small differences in drug release profile at 60.72% and 95 hrs. In vitro drug releases of polymeric micelles at pH 7.4 and 5.5 are shown in figure 5.

Table 2: Drug release kinetics of erlotinib loaded polymeric micelles.

Erlotinib formulation	Mathematical models for drug release kinetics			
	Zero order(R^2)	First order (R^2)	Higuchi model (R^2)	Kors-Peppas model (R^2)
Pluronic F 68 micelles	0.8023	0.8425	0.9574	0.5913
Pluronic F 127 micelles	0.8155	0.8357	0.9715	0.6377
TPGS micelles	0.9662	0.9602	0.9723	0.7735

We used four different kinetic models to assess the experimental drug-release data in order to determine the mechanism of drug release from our formulations (Table 2). Based on regression coefficient analysis, we discovered that the models of Higuchi the best fits with drug-release kinetics data for all types of micelles. This finding suggests that diffusion was the primary mechanism underlying the release of erlotinib from the Polymeric micelle formulations.

Conclusion

The polymeric micelles were prepared using solvent diffusion followed by lyophilization process. The CMC value was found near to reported concentration value for each polymer to load the requisite amount of drug. The desired nanometer size was be obtained impart targeting efficiency at tumor site. The zeta potential value shows negative charge to accumulate at tumor tissue cell membrane. The optimum drug release profile was observed at blood pH 7.4 and pH 5 at tumor site. Comparatively Pluronic F 127 and TPGS shows better micellar size, entrapment efficiency and sustain release than Pluronic F68. Additionally, results also paves the door to formulate mixed micelles of Pluronic F 127 and TPGS which may be efficient nanocarriers for erlotinib.

Abbreviations

TPGS: Tocopheryl polyethylene glycol succinate 1000
EGFR:epidermal growth factor receptor inhibitor
PDI:polydispersity index
%EE: Percentage entrapment efficiency
%DL: Percentage drug loading
PEO: Polyethylene oxide
PPO: Polypropylene oxide
PEG: Polyethylene glycol
HPLC: High performance liquid chromatography
CMC: Critical micelles concentration
HLB: Hydrophilic lipophilic balance

Ethics Approval and Consent to Participate: Not applicable.

Human and Animal Right: No Animals/Humans were used during this research work. Hence no ethical clearance to be taken.

Conflict of Interest: The authors declare no conflict of interest.

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