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DESIGN AND CHARACTERIZATION OF ERLOTINIB NANOPARTICLES

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ABSTRACT

The aim of this study was to formulate and evaluate nine formulations of ERLOTINIB loaded PLGA nanoparticles homogenization followed by solvent evaporation technique by use of biodegradable and biocompatible polymer i.e. PLGA. The effect of different concentrations of polymer and stabilizer (PVA) on particle size, zeta potential, %EE and drug release was studied. PLGA was used in different concentration of 120 mg, 150 mg, and 200 mg. Preformulation studies of FTIR and DSC was done to determine possible interaction between the drug and excipients. A5 showed 75.14% of release after 72 h and followed the fickian diffusion pattern of kinetic. SEM image showed the spherical morphology of nanoparticles.

INTRODUCTION

As mortality due to cancer continues to rise, advances in nanotechnology have significantly become an effective approach for achieving efficient drug targeting to tumor tissues by circumventing all the shortcomings of conventional chemotherapy. During the past decade, the importance of polymeric drug delivery systems in oncology has grown exponentially [1]. In this regard, a wide range of submicron materials has been designed and engineered, especially for defeating cancer. Its applications expedite the development of contrast agents, therapeutics, drug delivery vehicles and theranostics. Nanoparticles for drug delivery applications have been composed of biodegradable and biocompatible polymers based on natural and/or synthetic materials [2].

The use of nanocarriers has resolved the undesirable characteristics of anticancer drugs such as low solubility and poor permeability in cells [3]. One extensively investigated polymer is poly lactic-co-glycolic acid (PLGA), synthetic thermoplastic aliphatic biocompatible polyester.

There are specific formulations based on PLGA and its related homopolymers, polylactic acid (PLA) and polyglycolic acid (PGA), which have been approved by the US Food and Drug Administration (FDA) for medical applications [4].

In the field of controlled drug delivery system, increasing attention is focused on biodegradable polymers such as PLGA because of its biodegradability and biocompatibility [5]. PLGA nanoparticles are colloidal polymeric drug carriers that hold promise for oral drug delivery which represents by far the most common and convenient route of administration and also offer many advantages over conventional oral dosage forms, such as enhancing the oral bioavailability of those poorly absorbed drugs, protecting the encapsulated drugs in the polymer network [6].

In this study, an attempt was made to formulation and characterization of water- insoluble drug *i.e.* ERLOTINIB in the form of PLGA based nanoparticles by use of emulsification followed by homogenization technique. The prepared nanoparticles were characterized with regard to particle size, poly-dispersity index, zeta potential, morphological character, encapsulation efficiency, *in-vitro* release and kinetic study.

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MATERIALS AND METHODS

Erlotinib was obtained as a gift sample from Hetero Drugs Limited, Hyderabad, India. PLGA was purchased from Lactel-Durect Corporation, USA. All other ingredients used were of analytical grade.

Preformulation Study: Preformulation studies such as FTIR and DSC were performed to determine the possible interaction between Erlotinib and the excipients used in the formulation of nanoparticles.

Preparation of Nanoparticles: PLGA nano- particles of Erlotinib were prepared by homogenization method [7, 8]. Preparation of loaded nanoparticles was based on the oil/water emulsification solvent evaporation method. Both polymer and the drug were dissolved in acetone as an organic solvent. The solvent should be organic, miscible in water and easily removed by evaporation [9]. The organic phase so formed was added dropwise to an aqueous phase, containing (Polyvinyl alcohol) PVA cold as a surfactant, using a high-speed homogenizer using digital ultra turrax S22 & T25 dispenser in an ice bath at 8000 rpm speed. The emulsion formed was magnetically stirred to evaporate acetone.

After evaporation of the solvent, the nanoparticles were recovered by centrifugation using REMI C- 24BL cold centrifuge. Based on the initial trials formulations were prepared using general full factorial design (Qsutra Minitab 17 software) with two factors and three levels **Table 1**. Composition of prepared nanoparticles was tabulated in **Table 2**.

TABLE 1: FACTORIAL DESIGN

Factors	Levels		
PLGA (mg)	120	150	200
PVA (%w/v)	1	1.5	2

TABLE 2: COMPOSITION OF ERLOTINIB LOADED PLGA NANOPARTICLES.

Formulation	PLGA (mg)	PVA (%w/v)	Organic Solvent (ml)	Tween 80 (%v/v)
A1	120	1%		
A2	150	1.5%		
A3	200	2%		
A4	120	1%		
A5	150	1.5%	5 ml	0.2%
A6	200	2%		
A7	120	1%		
A8	150	1.5%		
A9	200	2%		

Evaluation of Nanoparticles: The supernatant was collected after centrifugation and used for the determination of % encapsulation efficiency (%EE) [10]. Particle size distribution, polydispersity index, and zeta potential of all formulations was measured by dynamic light scattering using Malvern nano ZS-90.

%EE = (Total drug added - Drug present in the supernatant) / Total drug added × 100

***In-vitro* Release Study:** *In-vitro* diffusion studies for Erlotinib loaded nanoparticles were carried out by using the dialysis bag technique [11, 12, 13]. The compartment was under continuous stirring at 37 °C ± 0.5. The drug which diffuses from nanoparticles in phosphate buffer saline was periodically withdrawn and the same amount was replaced with fresh phosphate buffer saline (pH 7.4). The absorbance of samples was analyzed by UV spectrophotometer using Agilent Technologies Cary 60 UV-Vis at 332 nm.

***In-vitro* Kinetic Study:** The dissolution profile of all formulations were fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model to ascertain the kinetic modeling of the drug release [14-17].

Surface Morphology: Morphology of the prepared PLGA nanoparticle was observed by scanning electron microscope (SEM).

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RESULTS AND DISCUSSION

FTIR Spectroscopy: FTIR spectra of Erlotinib and the mixture of Erlotinib, PLGA and PVA showed that there was no possible interaction between
the drug, polymer, and stabilizer used in the nano-particle formulation. It is shown in **Fig. 1**.

Differential Scanning Calorimetry (DSC): The DSC thermogram of Erlotinib, PLGA and PVA showed that there is no significant interaction between the drug, polymer and stabilizer used in the formulation of nanoparticles. The thermogram is shown in **Fig. 2**.

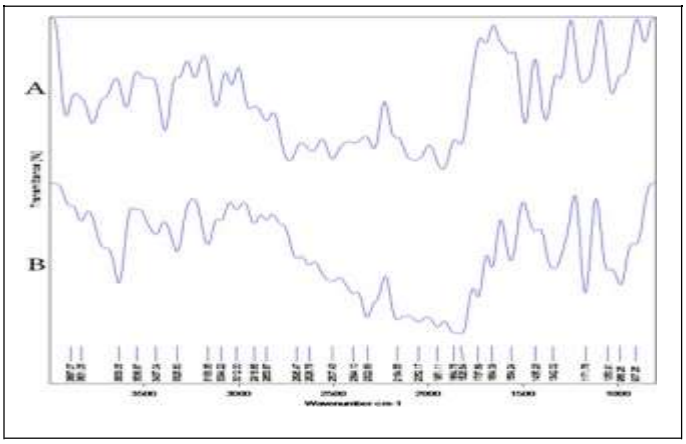

FIG.1: FTIRSPECTRAOFERLOTINIB LOADED PLGA NANOPARTICLES. A: Erlotinib. B: PHYSICAL MIXTURE OF Erlotinib + PLGA + PVA

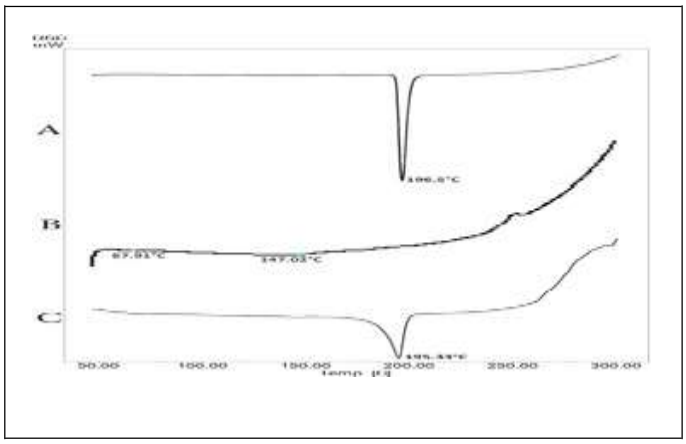

FIG. 2: DSC THERMOGRAM OF ERLOTINIB. B: DSC THERMOGRAM OF PLGA. C: DSC THERMOGRAM OF PHYSICAL MIXTURE OF Erlotinib + PLGA + PVA

Evaluation of the Nanoparticles: %EE, mean particle size, PDI and zeta potential of the prepared nanoparticles are shown in **Table 3**. The amount of drug with respect to the concentration of the PLGA nanoparticles had a significant effect on the loading efficiency. It was observed that an increase in the amount of polymer and concentration of stabilizer yields to increase in the amount of % EE. An increase in the size of nanoparticles with the increase in concentration of PLGA and PVA was observed. It was observed that by increasing the concentration of PVA as a stabilizer, zeta potential value got decreased. The reason is maybe due to presence of PVA at the surface of nanoparticles, it acts as a shield between nanoparticles and surrounding medium [18]. PDI value for all the prepared formulations found to be less than 0.3, indicating homogeneity of all formulations [19, 20].

TABLE 3: EVALUATION PARAMETERS OF ERLOTINIB LOADED PLGA NANOPARTICLES

Formulation	EE(%) ±SD	Particle Size (nm) ±SD	PDI ±SD	Zeta Potential (mV) ±SD
A1	20.30 ± 0.44	299 ± 16.99	0.13 ± 0.03	-8.45 ± 0.61
A2	58.61 ± 0.81	340 ± 7.80	0.15 ± 0.02	-2.98 ± 0.16
A3	62.91 ± 0.64	469 ± 7.99	0.20 ± 0.03	-2.99 ± 0.02
A4	49.96 ± 0.88	340 ± 6.34	0.11 ± 0.01	-3.44 ± 0.23
A5	64.37 ± 0.24	446 ± 3.71	0.14 ± 0.03	-2.50 ± 0.11
A6	71.46 ± 1.27	568 ± 1.49	0.21 ± 0.01	-3.26 ± 0.39
A7	52.19 ± 1.63	330 ± 2.66	0.19 ± 0.07	-2.40 ± 0.51
A8	58.54 ± 0.48	471 ± 3.27	0.21 ± 0.01	-2.05 ± 0.04
A9	73.18 ± 0.71	604 ± 6.48	0.14 ± 0.02	-1.42 ± 0.17

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Mean ± SD

***In-vitro* Release Study:** Release study was carried out for the formulations bearing % EE more than 55% for 72 h which shown in the following **Fig. 3**. A5 showed a higher release rate of 75.14 after 72 h. The release profile showed the initial burst release of 7.53% ± 2.12 for A5 which can be due to rapid dissolution of the adsorbed drug. After that, the slow release was observed on increasing the time duration and could be due to the penetration (diffusion) of release medium into the nanoparticles and dissolves the entrapped drug. A9 slow release rate was observed with results in an increase in the concentration of PLGA leads to tight and increase in the polymeric matrix around the entrapped drug.

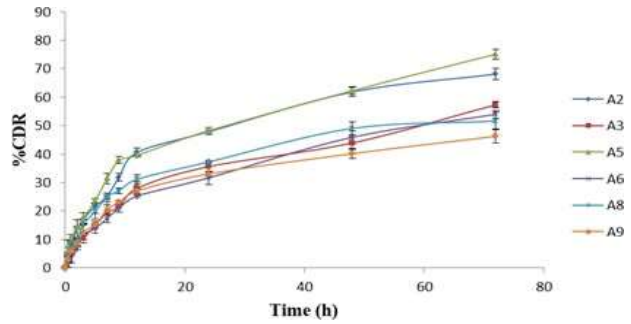

FIG. 3: CUMULATIVE DRUG RELEASE STUDY OF PLGA NANOPARTICLES (A2, A3, A5, A6, A8, A9)

Drug Release Kinetic: The drug diffusion profiles of all formulations were fitted into various kinetic modeling. From the result, it was obtained that all formulations were more linear towards Higuchi model with an R2 value of range 0.948 to 0.986 indicating that the drug release mechanism is by diffusion.

In Korsmeyer-Peppas model, the n values for all formulations were found to be close to 0.5 indicates fickian diffusion [21].

TABLE 4: RELEASE KINETIC DATA OF ERLOTINIB LOADED PLGA NANOPARTICLES

Formulations	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	n Value
A2	0.811	0.913	0.965	0.458
A3	0.881	0.943	0.986	0.497
A5	0.831	0.946	0.973	0.472
A6	0.885	0.941	0.989	0.469
A8	0.770	0.849	0.948	0.498
A9	0.791	0.849	0.975	0.518

SEM: Scanning electron microscope (SEM) was used to determine the surface topography of the ERLOTINIB loaded PLGA nanoparticles. The result is shown in **Fig. 4**. It was observed that the nanoparticles are spherical in shape with no agglomeration. for providing the facilities required for this project and their continuous support and inspiration.

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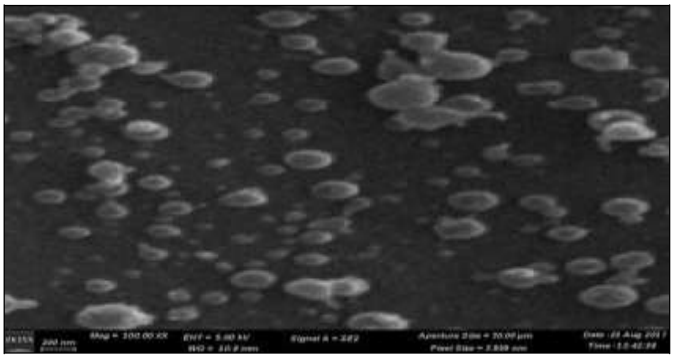
FIG. 4: SEM OF ERLOTINIB LOADED PLGA NANOPARTICLES IN 100KX



CONCLUSION

Nine formulations of Erlotinib loaded PLGA nanoparticles were prepared and evaluated. The best release pattern was obtained in A5 where 150 mg of PLGA and 1.5% w/v of PVA were used. The release pattern was best fitted to fickian diffusion, and sustained release drug delivery was obtained which could be applicable for cancer treatment.

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