FORMULATION AND EVALUATION OF GEFTINIB POLYMERIC   NANOPARTICLES

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ABSTRACT

The aim of this study was to formulate and evaluate nine formulations of GEFTINIB 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].

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In this study, an attempt was made to formulation and characterization of water- insoluble drug i.e. GEFTINIB 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.

MATERIALS AND METHODS

Geftinib 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 Geftinib and the excipients used in the formulation of nanoparticles.

Preparation of Nanoparticles: PLGA nano- particles of Geftini 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

Table2: COMPOSITION OF GEFTINIB 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 Geftinib 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.

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***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).

RESULTS AND DISCUSSION

FTIR Spectroscopy: FTIR spectra of Geftinib and the mixture of Geftinib, 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**.
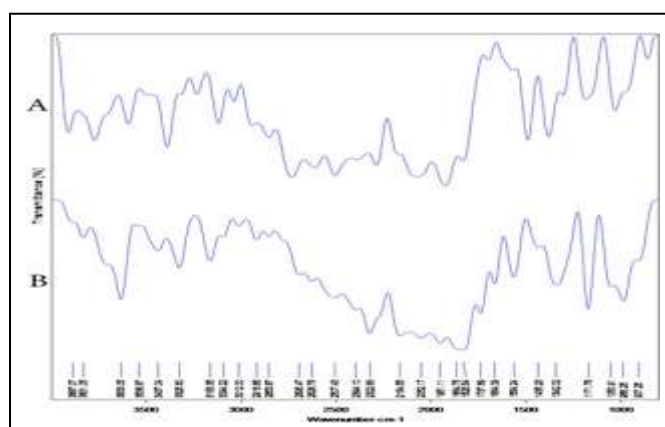

FIG.1:FTIR SPECTRA OF GEFTINIB LOADED PLGA NANOPARTICLES.   A: Geftinib. B: PHYSICAL MIXTURE OF Geftinib +PLGA + PVA

Differential Scanning Calorimetry (DSC): The DSC thermogram of Geftinib, 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**.
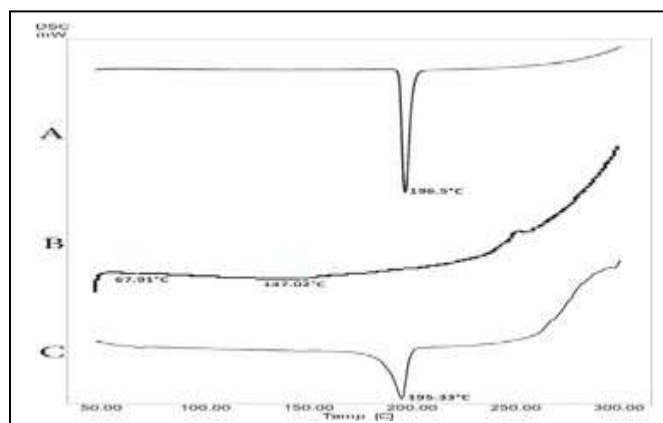

FIG. 2: DSC THERMOGRAM OF GEFTINIB. B: DSC THERMOGRAM OF PLGA. C: DSC THERMOGRAM OF PHYSICAL MIXTURE OF Geftinib + PLGA + PVA

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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 GEFTINIB 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

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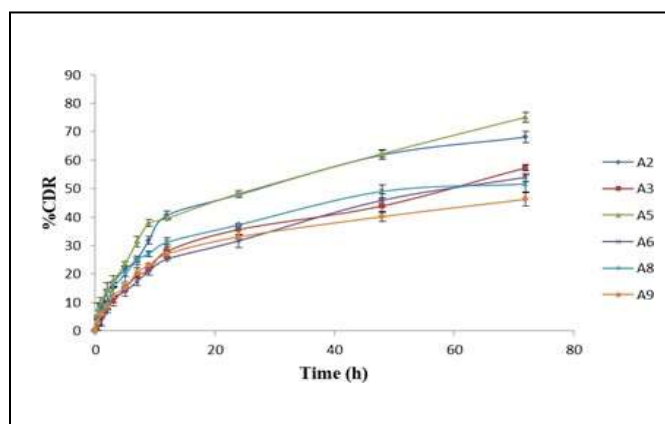
**FIG. 3: CUMULATIVE DRUG RELEASE STUDY OF PLGA NANOPARTICLES (A2, A3, A5, A6, A8, A9)**

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 R^2 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].

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TABLE 4: RELEASE KINETIC DATA OF GEFTINIB LOADED PLGA NANOPARTICLES

Formulations	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer-Peppas 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 GEFTINIB loaded PLGA nanoparticles. The result is shown in **Fig. 4**. It was observed that the nanoparticles are spherical in shape with no agglomeration.
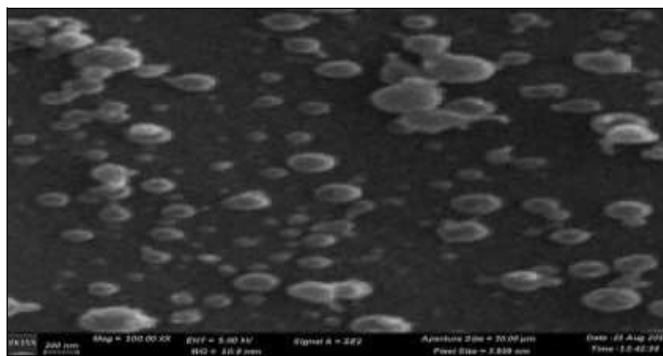
FIG. 4: SEM OF GEFTINIB LOADED PLGA NANOPARTICLES IN 100KX

For providing the facilities required for this project and their continuous support and inspiration.

CONCLUSION

Nine formulations of Geftinib 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.

REFERENCES

1. *Acharya S and Sahoo SK: PLGA nanoparticles containing various anticancer agents and tumour delivery by EPR effect. Advance Drug Delivery Reviews 2011; 18: 170-83.*
2. *Lai P, Daear W, Lobenberg R and Prenner EJ: Overview of the preparation of organic polymeric nanoparticles for drug delivery based on gelatine, chitosan, poly(d, l-lactide- co-glycolic acid) and polyalkylcyanoacrylate. Colloids and Surfaces B: Biointerfaces 2014; 118: 154-63.*
3. *Khan I, Gothwal A, Sharma AK, Kesharwani P and Gupta L and Iyer AK: PLGA nanoparticles and their versatile role in anticancer drug delivery. Critical Reviews in Therapeutic Drug Carrier System 2016; 33: 159-93.*
4. *Rezvantalab S, Drude NI, Keshavarz MM, Guvener N, Koons EK and Shi Y: PLGA-based nanoparticles in cancer treatment. Frontiers in Pharmacology 2018; 9: 1260.*
5. *Lamprecht A, Ubrich N, Yamamoto H, Schafer U, Takeuchi H and Maincent P: Biodegradable nanoparticles for targeted drug delivery in treatment of inflammatory bowel disease. Journal of Pharmacology and Experimental Therapeutics 2001; 299: 775-81.*
6. *Li X, Xu Y, Chen G, Wei P and Ping Q: PLGA nanoparticles for the oral delivery of 5-Fluorouracil using high pressure homogenization emulsification as the preparation method and in-vitro/in-vivo studies. Drug Development and Industrial Pharmacy 2008; 34:107-15.*

7. Sharma N, Madan P and Lin S: Effect of process and formulation variables on the preparation of parenteral paclitaxel-loaded biodegradable polymeric nanoparticles: A co-surfactant study. Asian Journal of Pharmaceutical Sciences 2016; 11: 404-16. Nagavarma B, Hemant K, Ayaz A, Vasudha L and Shivakumar G: Different techniques for preparation of polymeric nanoparticles-a review. Asian Journal of Pharmaceutical and Clinical Research 2012; 5: 16-23.

8. Thioune O, Fessi H, Devissaguet J and Puisieux F: Preparation of pseudolatex by nanoprecipitation: influence of the solvent nature on intrinsic viscosity and interaction constant. International Journal Pharmaceutics 1997; 146: 233-38.

9. Chen Y, Zhang W, Huang Y, Gao F and Xianyi S: Pluronic based functional polymeric mixed micelles for co delivery of doxorubicin and paclitaxel to multidrug resistant tumour. International Journal of Pharmaceutics 2015; 488: 44-58.

10. Yan GP, Zong RF, Li L, Fu T, Liu F and Yu XH: Anticancer drug loaded nanospheres based on biodegradable amphiphilic ε-caprolactone and carbonate copolymers. Pharmaceutical Research 2010; 27: 2743-52.

11. Chidambaram N and Burgess DJ: A novel in-vitro release method for submicron sized dispersed systems. AAPS Pharm Sci 1999; 1: 32-40.

12. Kumaresan C and Satishkumar K: Development of an inhaled sustained release dry powder formulation of salbutamol sulphate, an anti-asthmatic drug. Indian Journal of Pharmaceutical Sciences 2016; 78: 136-42.

13. Arifin DY, Lee LY and Wang CH: Mathematical modeling and simulation of drug release from

14. microspheres: Implications to drug delivery systems. Advance Drug Delivery Reviews 2006; 58: 1274-25.

15. Dash S, Murthy PN, Nath L and Chowdhury P: Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica Drug Research 2010; 67(3): 217-23.

16. Gautam S and Mahaveer S: Review: in-vitro drug release characterization models. International Journal of Pharmaceutical Research 2011; 2: 77-84.

17. Higuchi T: Mechanism of sustained action medication, Theoretical analysis of rate release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences 1963; 52: 1145-49.

18. Anudeep B, Ashwini HM and Goli D: Fabrication of PLGA nanoparticles of ropinirole HC by emulsion solvent evaporation technique to target brain. Word Journal of Pharmaceutical Research 2018; 7: 455-69.

19. Worldwide, M.I. Dynamic Light Scattering, Common Terms Defined; Inform White Paper; Malvern Instruments Limited: Malvern, UK, 2011; 1-6.

20. Nobbmann U and Morfesis A: Light scattering and nanoparticles. Materials Today 2009; 12:52-54.

21. Gouda R, Baishya H and Qing Z: application of mathematical models in drug release kinetics of carbidopa and levodopa ER tablets. Journal of Developing Drug 2017; 6: 2.