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Priyangi Roy
Department of Pharmaceutics, Gayatri College of Pharmacy, Sambalpur, India., priyangiroy8@gmail.com

Asok Kumar Samanta
Department of Pharmaceutics, Gayatri College of Pharmacy, Sambalpur, India.,
asokksamanta@rediffmail.com

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Preparation of Gefitinib Loaded Polycaprolactone Microcapsule For Controlled Release Drug Delivery System

Priyangi Roy, Purusattam Gartia, Aritra Nayek & Asok Kumar Samanta
Department of Pharmaceutics, Gayatri College of Pharmacy, Sambalpur, India.
Email:priyangiroy8@gmail.com; asokksamanta@rediffmail.com

Abstract - The aim of the study was to prepare gefitinib-loaded polycaprolactone microcapsules by simple conventional solvent evaporation method with a view to achieve controlled release of the drug following subcutaneous administration once in a week for targeted therapeutic action especially locally. The microcapsules were prepared using different drug-polymer ratios (1:2, 1:4 and 1:6) and three different stabilizers/surfactants (0.25% w/v, 0.50% w/v and 0.75% w/v) concentrations in aqueous phase. Depending upon the formulation variables, the highest drug entrapment efficiency and the lowest average particle size diameter of the microcapsules were found to be respectively 90.19±2.61 % and 201±3.05 µ. Comparison of Fourier Transform Infra Red spectra of gefitinib, polycaprolactone, their physical mixture and the drug- loaded microcapsules showed the absence of drug -polymer interaction .The in-vitro dissolution study showed that the release of drug from the microcapsules was almost complete on day seventh and the drug release followed Higuchi model.

Keywords- *Gefitinib, Polycaprolactone, Microcapsules, Controlled release, Targeted therapeutic action.*

I. INTRODUCTION

Gefitinib (Iressa, ZD1839), a potent high-affinity competitive tyrosine kinase inhibitor reacts primarily at epidermal growth factor receptor (EGFR) and hence used in the treatment of advanced non-small cell lung cancer (NSCLC), breast, pancreatic, ovary and colon cancer [1-4].

Polycaprolactone (PCL), a biodegradable, biocompatible, and synthetic semicrystalline polymer having a very low glass transition temperature is suitable for long-term controlled drug delivery [5, 6].

The objective of the present study was to develop and characterize gefitinib-loaded polycaprolactone microcapsules for controlled release of the drug. The microcapsules were prepared by conventional solvent evaporation method and the effect of drug-polymer ratios and the concentration of polyvinyl alcohol which was used as stabilizer on the characteristic of the microcapsules were evaluated.

II. MATERIALS AND METHOD

Gefitinib (Miracalas Pharma Pvt. Ltd. and Naprod Life Science Pvt. Ltd.Mumbai, India) was obtained commercially. Polycaprolactone (ALDRICH,# MKBB 6776, M.W. 14,000); Polyvinyl alcohol (CHEMIE, M.W. 1,15,000); Chloroform (FINAR, MW. 119.38); Potassium di- hydrogen phosphate (RANKEM, PM 002-02); Disodium hydrogen phosphate (RANKEM, SP001-02); Sodium lauryl sulphate (MERCK) were purchased commercially.

METHOD

Preparation of microcapsules

Gefitinib-loaded PCL microcapsules were prepared by simple conventional solvent evaporation technique. Required amount of polymer was dissolved in 2 ml chloroform. Gefitinib was added and stirred continuously until dissolved in the polymer solution. The oily phase was added slowly in a thin stream with stirring into aqueous PVA solution which was stirred at a moderate rate. The stirring was continued for three hours at room temperature. After evaporation of solvent, the microcapsules thus formed were collected by filtration, washed with sufficient amount of double glass distilled water, and left at room temperature. Then the microcapsules were vacuum dried for five days and finally stored at a desiccator until used. Blank microcapsules without Gefitinib were also prepared and processed in the same way.

Determination of Entrapment Efficiency

A calibration curve of Gefitinib was plotted using different dilutions of the drug (5 to 80 µg/ml) in glacial acetic acid analyzing spectrophotometrically (UV-VIS spectrophotometer 1700 Pharma Spec, Shimadzu, Japan) at 340.5 nm.

A known amount of microcapsules was dissolved in glacial acetic acid. An aliquot, following suitable dilution, was analyzed at 340.5 nm and the amount of drug in the microcapsules was calculated from the standard curve. The % of drug entrapment efficiency was calculated by using the following equation:

Drug entrapment efficiency (%) = (Actual drug content /Theoritical drug content) ×100

Determination of particle size

Particle size of the microcapsules was determined by optical microscopy using at least 100 MC.

Invitro drug release

A static dissolution method was adapted for the determination of the in-vitro release of gefitinib from the MC.

Briefly: 0.05 M phosphate buffer pH 7.4 ±0.05 containing 0.23 % w/v of Sodium lauryl sulphate was used as dissolution medium for gefitinib release study. The accurate amount of MC was added in the dissolution medium kept in a 20 ml capacity of scintillated screw capped bottle. The bottles were kept in an incubator at 37 ±0.5 ^{o}C with occasional shaking throughout the dissolution study. 5.0 ml sample solution was withdrawn from the bottle at a predetermined time and equal amount of fresh medium was replaced into the bottle. The aliquot was filtered through a 0.45 µ membrane filter and analyzed spectrophotometrically at 345.5 nm. The amount of the released drug was determined from the standard graph drawn in the dissolution medium at a wavelength 345.5 nm

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of pure gefitinib, polycaprolactone, physical mixture and the Gefitinib-loaded PCL microcapsules were obtained from Fourier Transmission Infra Red Spectrophotometer (IR Prestige -21, FTIR, Shimadzu ,Japan). Known amount of the samples were mixed with KBr , pressed into disc and scanned from 4000 cm $^{-1}$ to 400 cm $^{-1}$.

Differential Scanning Calorimetry (DSC)

DSC study of pure gefitinib, polycaprolactone, physical mixture and the selected microcapsules were performed in a Differential Scanning Calorimeter (DSC-60, Shimadzu). Accurately weighed amount of each sample was heated in the range of 30 to 300 ^{0}C at a scanning rate 10 ^{0} C /min using inert nitrogen gas and the thermograms were recorded and characterised.

III. RESULT AND DISCUSSION

Gefitinib loaded Microcapsules Preparation, Particle size and Entrapment Efficiency

Gefitinib loaded microcapsules were found to be discrete. Depending upon the formulation variables, the mean particle size (MPS) ranged from 201±3.05 to 239.66±2.51 µ and the % drug entrapment efficiency (DEE) varied from 21.93±2.15% to 90.19±2.61%. The surfactant concentration influenced both the particle size and DEE of the microcapsules. It is observed that as the surfactant concentration increased the size of the particle and DEE decreased (data not shown). This may be due to higher movement of gefitinib into the surfactant solution.

Based on higher DEE and lower particle size, the microcapsules prepared using drug: polymer in a ratio of 1:4 and 0.25w/v polyvinyl alcohol in the aqueous phase were selected for drug release study. The particle size affects the biopharmaceutical, physicochemical as well as drug release properties from the MCs.

Invitro Drug release studies

The drug release profile (Fig.-1) showed that after an initial burst effect, the drug was released in a controlled fashion for about five days. As the crystallinity of the polymer has not been changed (Fig.3) in the formed MC, the diffusion mechanism of the polymeric membrane had not been modified resulting the controlled release of gefitinib for longer time.

Fourier Transmission Infra-red Spectroscopy (FTIR)

FTIR spectrum of gefitinib (Fig.2, A01) revealed the characteristic stretching of O-H band at 3398.57 cm^{-1} (3700-3350 cm^{-1}); methoxy group peak at 2825.22 cm^{-1} (2850-2815 cm^{-1}); the most characteristic aromatic skeleton vibration at 1606.70 cm^{-1} (1610-1590 cm^{-1}) for aromatic compound ; N-H stretch band at 3398.57 cm^{-1} (3500-3300 cm^{-1}); aromatic C-N peak at 1330.88 cm^{-1} , 1292.31 cm^{-1} ,1265.30 cm^{-1} , (1350-1250 cm^{-1}) (Fig.2.A.1) The characteristic peaks of the drug were also found in the spectra of physical mixture (Fig.2.A3) and the formed MC(Fig.2.A4).

Again the FTIR spectrum of PCL(Fig.2,A02) , the aliphatic compound [7,8], showed the characteristic methylene (CH2-)n rocking n≥3 peak at 731.02 cm^{-1} (750-720 cm^{-1}) and six –membered ring lactone peak at 1725 cm^{-1} existed in A3 and A4 of Fig.2.[9].

Differential Scanning Calorimetry (DSC)

DSC thermograms give information on the physical properties like crystalline and amorphous state of samples. Here the thermograms of gefitinib (Fig. 3, 1) showed an endothermic peak at 193.31 ^{0}C corresponding to its melting point temperature. However, the peak was not detected in the thermograms of gefitinib loaded MC (Fig 3, 4) and also in the physical mixture of gefitinib and PCL (Fig.-3, 3). As the drug did not show its endothermic peak in the MC, it may be said to be converted into the amorphous state [10].Hence it may be concluded that in both the cases i. e. ; in the physical mixture of drug and polymer and in the formed MC , the drug is in the amorphous state and has been homogenously distributed in the PCL matrix [11].The existence of drug in the microcapsules and in the physical mixture of drug and polymer at their formed ratio was confirmed by the FTIR (Fig.2,A3 and A4) study. The crystallinity of the PCL (peak at 68.95 ^{0}C) (Fig. 3,2) was not remarkably changed in the physical mixture of drug and polymer (peak at 67.26 ^{0}C) (Fig 3,3) and also in the formed MC **(**peak at 66.26 ^{0}C) **(**Fig. 3, 4) This indicates that mechanism of diffusion of the drug through the polymeric membrane did not change throughout the dissolution study.

IV. CONCLUSION

Gefitinib- loaded Polycaprolactone microcapsules prepared by the simple coventional solvent evaportion method had the highest 90.19±2.61 DEE, spherical shape and lowest particle size diameter 201±3.05 µ. The drug polymer ratio and the surfactant concentration had influenced the DEE and particle size of the formed capsules.The DSC thermogram showed that the drug was homogenously distributed into the polymer matrix in amorphous form and the crystallinity of PCL not been changed.

The FTIR study showed the presence of drug in the microcapsules and in the physical mixture of drug and polymer indicating the absence of incompatibility of the drug with the polymer. The in-vitro drug release study showed that the drug was released till day seventh and followed Higuchi model. This preliminary study could be substantiated further by animal study.

V. ACKNOWLEDGEMENT

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VI. REFERENCES

[1] Ciardiello F, Caputo R, Bianco R, Damiano V, Pomatico G, De Placido S, Bianco AR, Tortora G. , Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. Clinical Cancer Research, 6, 2000, 2053-2063.

[2] Yan Y, Lu Y, Wang M, Vikis H, Yao R, Wang Y, Lubet RA, You M., Effect of an Epidermal growth factor receptor inhibitor in mouse models of lung cancer. Mol Cancer Res., Dec, 4(12), 2006, 971-81.

[3] Li J, Kleeff J, Giese N, Buchler MW, Korc M, Friess H. Gefitinib ('Iressa', ZD1839), a selective epidermal growth factor receptor tyrosine kinase inhibitor, inhibits pancreatic cancer cell growth, invasion, and colony formation. Int J Oncol, Jul, 25(1), 2004, 203-10.

[4] Cohen MH.,William GA, Sridhara R,Chen G, Pazdur R., FDA Drug approval summary : Gefitinib (ZD 1839) (Iressa(R)) tablets. Oncologist, 8, 2003, 303-306.

[5] Sinha VR, Bansal, K, Kaushik, R, Kumria, R, Trehan A., Polycaprolactone Microspheres and Nanospheres: an overview. International Journal of Pharmaceutics, 278, 2004, 1–23.

[6]. U.Edlund, A.C. Albertsson, Degradable Polymer Microspheres for Controlled Drug Delivery, Advances in Polymer Science, Springer-Verlag Berlin Heidelberg, Vol. 157, 2002, 67 -112.

[7]. Williams; Richard S. , Polyester moulding compositions, Patent No.4540729**,** September 10, 1985.

[8]. B. K. KIM, S. J. HWANG, J. B. PARK, & H. J. PARK, Characteristics of felodipine-located poly(*e*-caprolactone) Microspheres. Journal of Microencapsulation, 22(2), March 2005, 193-203.

[9]. John Coates, Interpretation of Infrared spectra, a practical approach. Encyclopedia of Analytical Chemistry. R. A. Meyers (Ed.). John Wiley & Sons Ltd, Chichester, 2000, Pp.10815-10837.

[10]. Dillen, K., Vandervoort, J., Van den Mooter, G., Verheyden, L., Ludwig, A., Factorial Design, physicochemical characterisation, and activity of ciprofloxacin-PLGA Nanoparticles. International Journal of Pharmaceutics, Vol. 275, No. 1, 2004, 171-187.

[11]. Mainardes RM, Evangelista RC, Praziquantel-loaded PLGA nanoparticles: preparation and characterization. J. Microencapsulation , Feb. 22(1), 2005,13-24.

Higuchi model

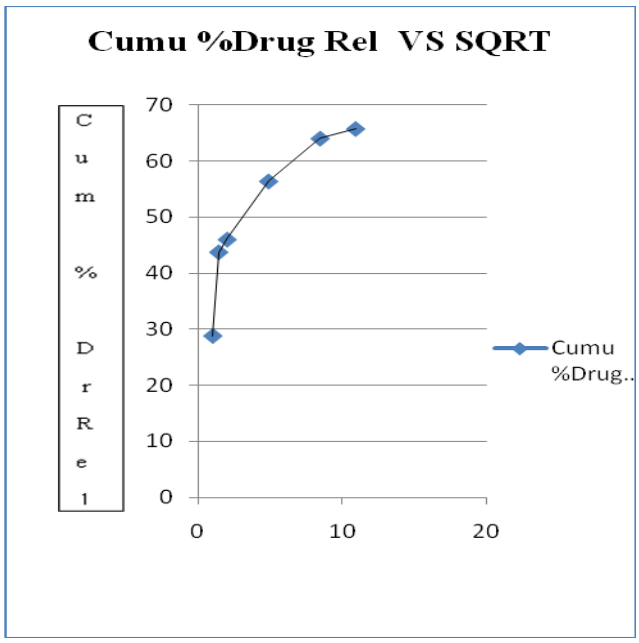

Figure1. Drug release profile of Microcapsules of Batch no. R4

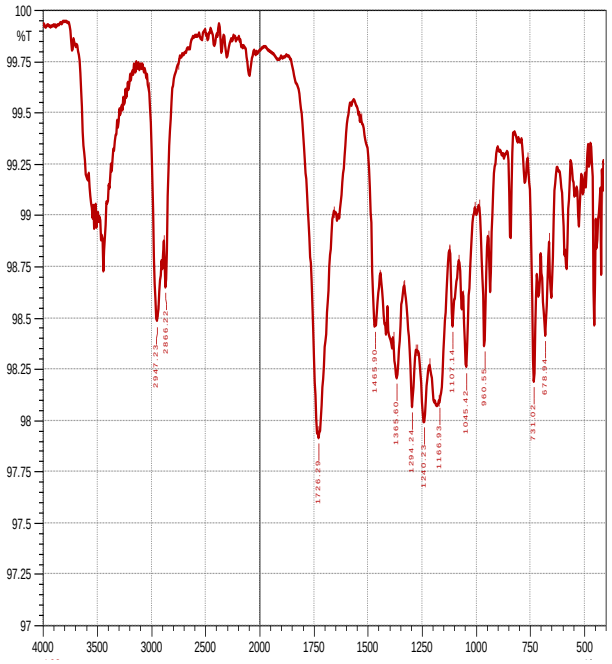

Figure2. FTIR spectra of AO2: PCL

IR STUDY

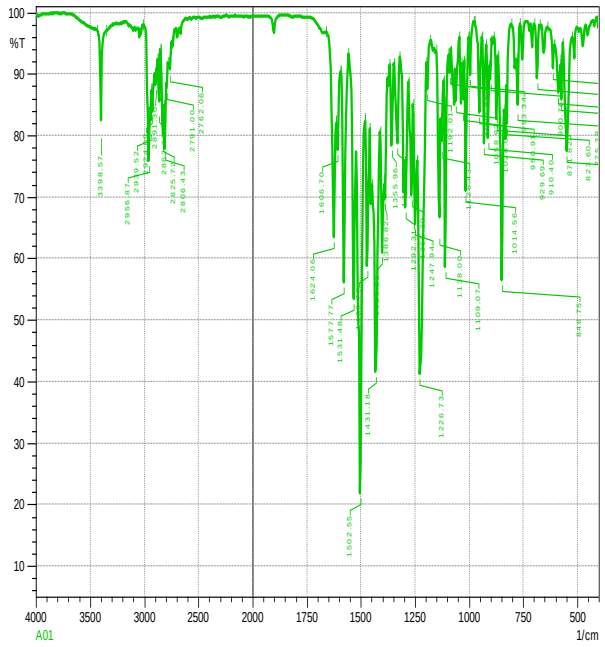

Figure2. FTIR spectra of AO1: gefitinib

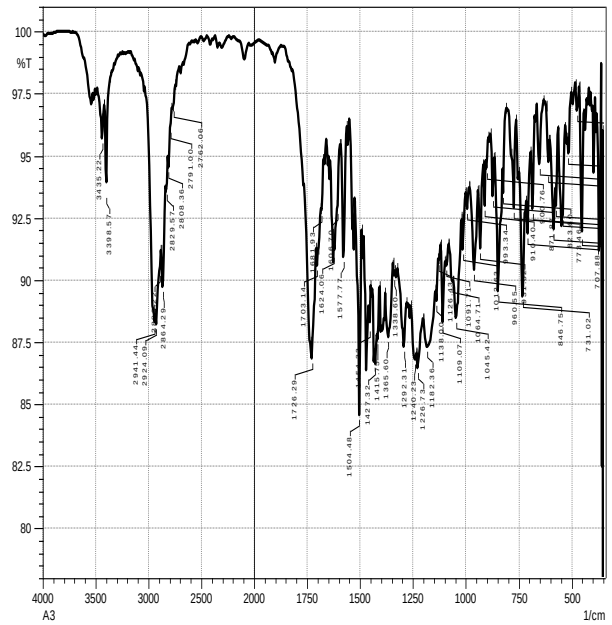

Figure2 FTIR spectra of A3 Physical mixture of DP

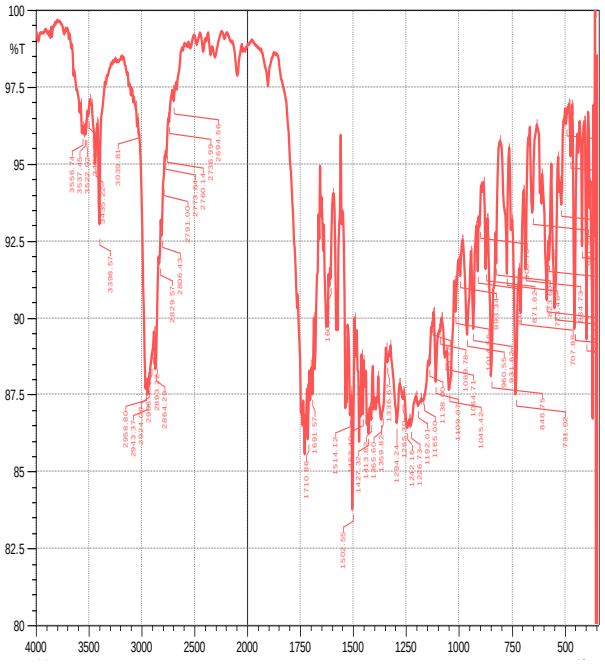

Figure2. FTIR spectra of A4: Formed MC

DSC Study

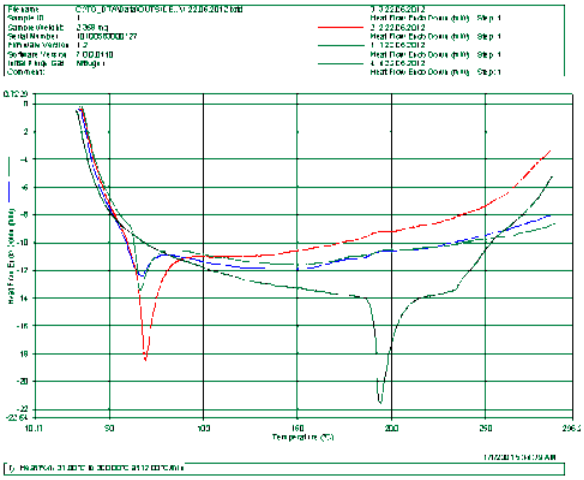

Figure 3. DSC curve of 1: Gefitinib (D); 2: PCL (P);

3: Physical mixture of DP and 4: Formed MC

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