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Effect of α- Cyclodextrin on Gefitinib

KEYWORDS: α-Cyclodextrin, Gefitinib, Absorption, Emission, Phase solubility

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ABSTRACT *Gefitinib is a drug used in the treatment of metastatic epethilial cell lung cancer. This Study examined the complexation of Gefitinib with α-Cyclodextrin in liquid State. The inclusion processes are discussed based on absorption, emission and phase solubility studies. The absorption and emission maxima of gefitinib appear at 263nm and 402nm. The stability constant [Kst] of Gefitinib is calculated.. The formation constant [K] value is calulated by analysing in the intensities of absorption and emission maxima with the α-CD concentration.*

Introduction

Gefitinib is a drug used for the treatment of epithelial cell lung cancer . It is taken in 250mg oral doses once daily, higher doses showing no improvement but increased toxicity .It is an anilinoguinazoline with chemical name N-[3-chloro-4-fluoro-phenyl-7-methoxy-6-[3-morpholin-4-yl propoxy] quinazoline 4- amine. It has the molecular formula C_{22} H_{24} $ClFN_4$ O_3 , a relative molecular mass of 446.9[1]

Gefitinib is the first selective inhibitor of epidermal growth factor receptor's [EGFR] tyrosine kinase domain .Thus gefitinib is an EGFR inhibitor[2,3]

Cyclodextrins

Cyclodextrins (CD) are a group of structurally related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface. The most commonly used host molecules are cyclodextrins[4].Cyclodextrinsare cyclic oligosaccharides of 6, 7 or 8 -D-glucopyranoseunits with alteratively hydrophobic central cavity and hydrophilic outer surface [5,6] . The hydrophobic CDs innercavity forms inclusion complexes with a wide range of guest molecules[7,8] while the hydrophilic exterior enhances CD solubility in water.CDs are classical examples of compounds that can form inclusion complexes[9]

Experimental

Appratus

- Double beam spectrophotometer-2203
- Jascospectrofluorometer FP-8200
- Rotary shaker

Procedure for preparation of liquid inclusion complex of Gefitinib with α-CD

The solutions of the stock ofgefitinib was transferred into 10ml volumetric flasks containing 0.002,0.004,0.006,0.008, and 0.01moldm^{-3} α-CDsolution. The mixed solution was diluted to 10ml with double distilled water and shaken thoroughly.The absorption and fluorescence spectra were recorded.

Phase solubility studies:

Phase solubility studies were performed according to the method reported by Higuchi and Connors[10] . Guest compound in constant amounts that exceeded its solubility was transferred to screw capped vials containing 15ml of aqueous solution of α-CD .The contents were stirred on rotary shaker for 72hrs at 37°C.The time duration was fixed based on pilot experiment and found to be sufficient to achieve equilibrium of mixture .After reaching equilibrium samples were filtered through the whatmann No.1 filter paper and analysed by UV-Visible Spectrophotometer.Solubility studies were performed in triplicate.

Results and Disscusion

Table:1

Absorption and Fluorescence maxima of Gefitinib at different concentration of α-CD

α-CD con	λ max	Absorbance	Δflu	Intensity	1/(αCD)	Log ε
0	263.0	0.392	402	102.275		4.00
0.002	262.0	0.443	404	106.316	500	4.05
0.004	261.0	0.543	405	107.632	250	414
0.006	260.5	0.601	407	109.820	166.66	4.18
0.008	259.5	0.633	409	110.654	125	4.21
0.01	259	0.705	411	111.542	100	4.25

Table (1) and figure (1,2) shows the absorption and fluorescence maxima of Gefitinib solutions containing various concentrations of α-CD.The absorption maxima of gefitinib appear at 263.0nm.The absorption intensities are increased with the increasing concentration of α-CD. As theconcentration of α-CD increases the absorption wavelength is blue shifted from 263nm-259nm.It is already reported that the anions are blue shifted in the α-CD medium[11]. Herebecause of the presence of halide ions the absorption maxima is blue shifted.The fluorescence maxima of gefitinib appear at 402nm. Upon increasing the concentration of α-CD it is shifted from 402nm to 411nm.By theaddition of α-CD the fluorescence and their intensities are red shifted.

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Figure.1
Absorption spectra ofGefitinib at different concentration of α-CD

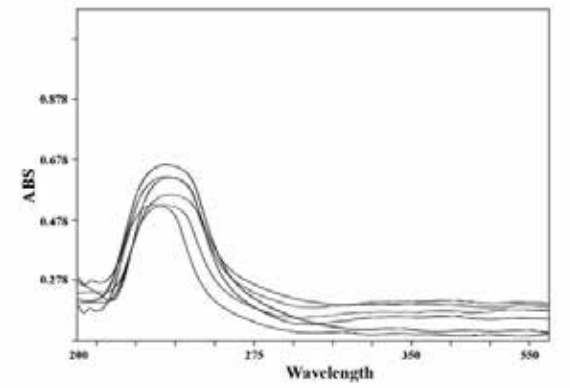


Figure.2
Fluorescence spectra of Gefitinib at different concentration of α-CD

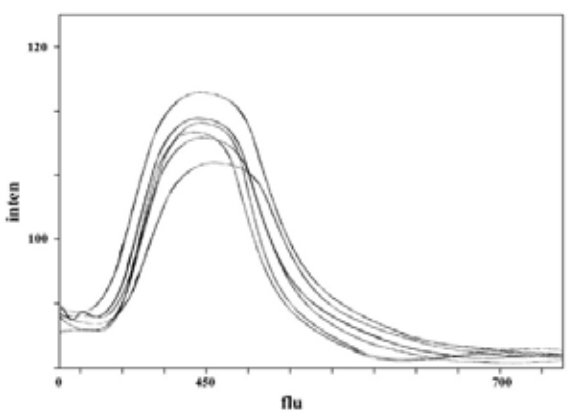
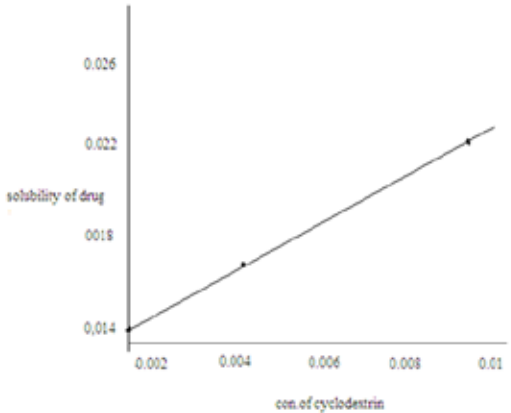


Figure.3
Phase solubility ofGefitinibat different concentration of α-CD



The phase solubility diagram of gefitinib as a function of concentration of various CDs at room temperature is shown in fig.3.The solubility of gefitinibwith an increase in concentration of CDs gives an AL type of phase solubility diagram . The stability constant (Kst) of the complex was calculated from the slope and intercept (So) of the phase solubility diagram according to the equation

Kst = slope/So(1-slope)

The Kstvalue ofgefitinib α-CD complex was calculated to be 87.30M^{-1}. The Kst values of α-CD gefitinib complex make them suitable for practical applications interms of improving the drug permeability solubility related oral bioavailablity.

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