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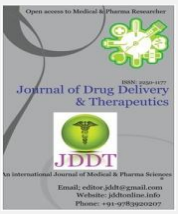

Open Access Research Article

SOLUBILITY ENHANCEMENT OF EFAVIRENZ (BCS CLASS II DRUG) BY CYCLODEXTRIN INCLUSION COMPLEX TECHNIQUE

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ABSTRACT

The solubility of BCS class II drugs can be enhanced using inclusion complex techniques. Cyclodextrin (CD) and its derivatives are promising carrier for the enhancement of aqueous solubility of drugs. The use of the Kneading technique to obtain solid inclusion system permitted the formation of a uniform, substantially non-crystalline particle, which increased the solubility and stability of Efavirenz (EFV). The present work shows the enhancement of aqueous solubility of BCS class II drug i.e. EFV by making inclusion complex with β-CD. The aqueous solubility of EFV is calculated to be 5± 0.003 µg/ml which was increased up to 288.9±0.005 µg/ml when complexed with β-CD in ratio of 1:1 and 318.5± 0.03 µg/ml in ratio of 1:2. This shows that, the inclusion complex technique is a promising way to enhance aqueous solubility.

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INTRODUCTION:

The process of drug absorption, bioavailability and pharmacokinetic profile of orally administered drug substance is highly dependent on factor solubility and permeability of that compound in the aqueous medium. The study of drug synthesis in pharmaceutical researches involves the maximum number of lipophilic drugs which have very low solubility rate[1]. Efavirenz (EFV) [(S)-6-chloro-4-(cyclopropyl ethynyl)-1, 4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one] is a non-nucleoside reverse transcriptase inhibitor approved for the treatment of human immunodeficiency virus type 1 infection. Efavirenz is a drug with crystalline lypophillic solid whose molecular mass is 315.68 and aqueous solubility of 9.0µg/ml. This is a class II drug (low solubility, high permeability) that is highly permeable, poorly soluble drugs often demonstrate poor gastrointestinal (GI) absorption due to inadequate drug solubility in GI fluids [2].

The solubility of these low soluble drugs is being enhanced by various modifications. Cyclodextrins (CD's) are the cyclic oligosaccharides containing 6(α-CD), 7(β-CD), 8 (γ-CD) α- 1, 4-linked glucopyanose units. Each of these CD molecules has the hydrophilic property which is helpful in form of hydrophobic guest molecule [3].

MATERIALS AND METHODS:

Materials

EFV drug provided by Shagun Pharma, Indore. Cyclodextrin is used of Loba chemie.

Methods

Preparation of Calibration Curve of Drug Efavirenz in distilled water:

The calibration curve was made by finding the absorbance of drug dilutions at different concentration in the distilled water (solvent).Initially 10 mg of drug was dissolved in 10 ml ethanol as a stock solution. Further dilutions were prepared having strength of 5, 10, 20, 25, 30, 40 µg/ml and diluted with distilled water.

Saturated solubility:

The saturated solubility of EFV alone in distilled water was determined. Sufficient excess amount of EFV was added to 10 ml glass vials containing distilled water. The vials were shaken mechanically for 12 h on mechanical shaker (Lab Hosp, Mumbai) at 37 ± 2°C. The solutions were allowed to equilibrate for next 24 h. The solution was transferred into eppendorf tubes and centrifuged for 5 min at 2000 rpm. The supernatants of each vial were filtered through 0.45µ membrane filter and analyzed for drug content by UV visible spectrophotometer (UV-1800, Shimadzu, Japan) at 248 nm after appropriate dilutions. The study was performed in triplicate.

Phase Solubility Studies of Efavirenz with Cyclodextrin:

For the determination of Phase Solubility, different concentration of cyclodextrins in Mili Molar (1,2,4,6,8,10,12 mM) solution form were prepared in 10ml distilled water each containing approximate 30mg of Efavirenz in each solution.

Preparations of Inclusion Complex with help of Cyclodextrin:

Basically inclusion complex is the combination of drug and the cyclodextrins was prepared by kneading method.

Kneading Method:

Initially Cyclodextrin was taken in a mortar with 1 ml of 50% ethanol to prepare slurry, then Efavirenz in the same equimolar quantity of cyclodextrin was taken and triturated well for mixing. Small amount of water is then added to make slurry having proper consistency and kneaded for 15 min, and dried at 50°C for 24 h. The resultant dry solid mass was powdered well, passed through 60# sieve and stored in a sealed glass vials.Inclusion complexes were prepares in the ration of 1:1 and 1:2 of drug to cyclodextrin ratio [4].

RESULTS AND DISCUSSIONS:

Calibration curve of drug Efavirenz

The λ_{max} of EFV in distilled water was calculated as 248 nm.

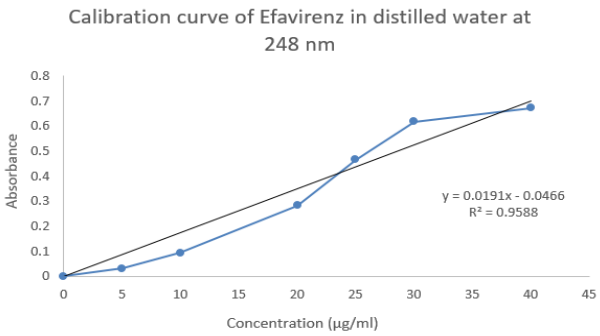

Figure 1: Calibration curve of Efavirenz in distilled water at 248 nm

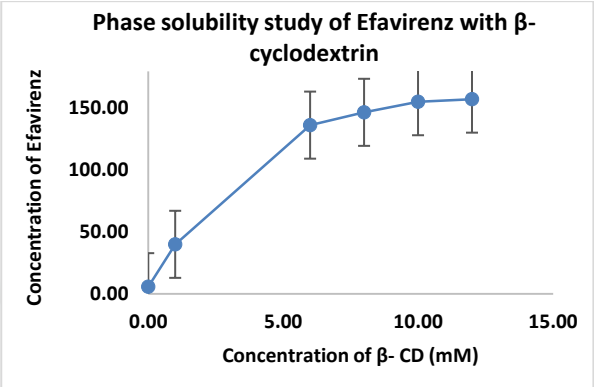

Figure 2: Phase solubility study of Efavirenz with β-CD (K_{st} = 190.05 M^{-1})

Phase Solubility Studies

Table 1: Phase Solubility Studies of Efavirenz with Cyclodextrin

Concentration of CD (mM)	F1	F2	F3	Average	Concentration (in µg/ml)	Concentration (Dilution factor)	SD
0.00	0.066	0.06	0.059	0.062	5.698	5.70	0.0030
1.00	0.708	0.721	0.71	0.713	39.979	39.98	0.0057
6.00	0.203	0.224	0.211	0.213	13.646	136.46	0.0086
8.00	0.222	0.236	0.239	0.232	14.681	146.81	0.0074
10.00	0.249	0.251	0.246	0.249	15.540	155.40	0.0020
12.00	0.258	0.252	0.248	0.253	15.751	157.51	0.0041

Solubility of drug efavirenz inclusion complex (1:1 and 1:2)

The solubility of prepared inclusion complexes in ratio 1:1 and 1:2 were determined by dissolving complexed overnight into the distilled water. It was observed that more amount of drug solubilized with the increase in amount of cyclodextrin. Following table shows the enhancement in the aqueous solubility of efavirenz with cyclodextrin complex.

Table 2: The Solubility of Drug Inclusion Complexes (1:1 and 1:2)

Complex Solubility	F 1	F 2	F 3	Average	Concentration	Conc* DF	Amount (µg/ml)
Without CD	0.066	0.06	0.059	0.061	5.668	5.668	5.668412
1:1	1.064	1.057	1.051	1.057	57.797	288.987	288.9878
1:2	1.129	1.209	1.173	1.170	63.713	318.568	318.5689

The results show that the initial solubility of efavirenz in water is equal to 5.66 µg/ml whereas, with cyclodextrin in the ratio of 1:1 it was observed as 288.9 µg/ml and 318.56 µg/ml with 1:2 drug: cyclodextrin complex.

CONCLUSION:

The solubility of BCS class II drugs can be enhanced using inclusion complex techniques. Cyclodextrin and its derivatives due to their high aqueous solubility are promising carrier for the enhancement of aqueous solubility of poorly soluble drugs. The use of the Kneading technique to obtain solid inclusion system permitted the formation of a uniform, non-crystalline particle, which increased the solubility of EFV, and provided an increase in the stability of the drug also.

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