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Research Article

Formulation development & invitro evaluation of efavirenz cyclodextrin complexes immediate release tablets

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Article History	Abstract
Received on: 01-11-2021 Revised on : 14-11-2021 Accepted on : 03-01-2022	<p>The study was designed to investigate the effect of cyclodextrins (CDs) on the solubility, dissolution rate, and bioavailability of efavirenz by forming inclusion complexes. Prepared inclusion complexes were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD) studies. <i>In vitro</i> dissolution study was performed using phosphate buffer pH 6.4, distilled water, and HCl buffer pH 1.2 as dissolution medium. Among all efavirenz-cyclodextrins complexes, efavirenz-DM-<math>\beta</math>-CD inclusion complex (1:3) prepared by coprecipitation method showed 1.53-fold and 4.11-fold increase in absorption along with 2.1-fold and 2.97-fold increase in dissolution rate in comparison with Pletoz-50 and pure efavirenz, respectively.</p>
<b>Keywords:</b> Bioavailability; efavirenz-CD inclusion complex; dissolution; solubility.	
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## Introduction

Cyclodextrins (CDs) are cyclic oligosaccharide consisting of at least six  $\alpha$ -(1-4)-linked glucopyranose units.  $\alpha$ -,  $\beta$ -, and  $\gamma$ -CD consist of six, seven, and eight glucopyranose units, respectively [2]. Exterior hydrophilic surface is favorable for enhancement of absorption rate through the gastrointestinal tract and the hydrophobic cavity generally provides a favorable environment for hydrophobic molecules or parts of a molecule thus improving the solubility of hydrophobic compounds in aqueous solutions [3, 4]. The solubilization abilities of CDs have been attributed to the formation of inclusion complexes be-

tween CDs and the "guest" molecules. Generally, this complexation involves the inclusion of the "guest" molecule in the cavity of the host molecule, such as CD, with no covalent bonding [5,6,7,8]. All these derivatized CDs offer better solubility, higher aqueous stability, and the increased bioavailability and have less undesirable side effects compared to natural CDs (9-12).

Efavirenz is a synthetic non-nucleoside reverse transcriptase (RT) inhibitor with antiviral activity. Efavirenz binds directly to the human immunodeficiency virus type 1 (HIV-1) RT, an RNA-dependent DNA polymerase, blocking its function in viral DNA replication. In combination with other antiretroviral drugs, this agent has been shown to significantly reduce HIV viral load, retarding or preventing damage to the immune system and reducing the risk of developing AIDS.

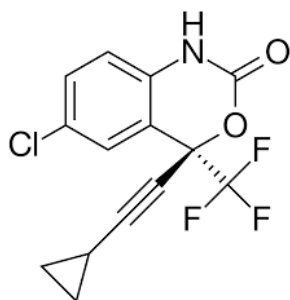


Figure1: Chemical structure of Efavirenz

## Material and Methods

### Materials

Efavirenz was generously provided by Cadila Pharmaceutical Laboratory, Ahmedabad, India, as a gift sample.  $\beta$ -CD was purchased from Hi-media Laboratories Pvt. Ltd. Mumbai. Hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) was obtained as a gift sample from Sun Pharma Advance Research Company, Vadodara, India.  $\gamma$ -CD and dimethyl- $\beta$ -cyclodextrin (DM- $\beta$ -CD) were procured as gift samples from Roquette Pharma, USA. 13

### Phase Solubility Study

The analytical method based on UV spectrophotometry was developed before starting the phase solubility study. The calibration curve was prepared by measuring the absorbance of standard methanolic solutions of efavirenz in the concentration range 5–50  $\mu\text{g}/\text{mL}$  at 257.00 nm.

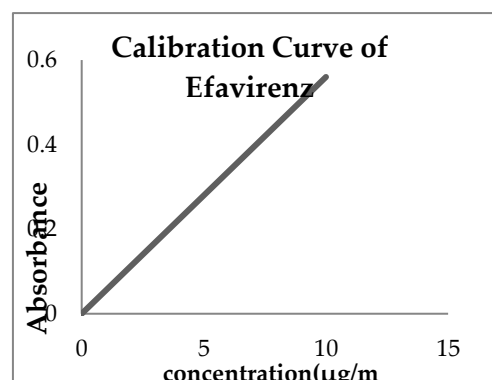
### Preparation of dissolution medium

**Standard solution:** 10 mg of efavirenz was taken in to a 10 ml volumetric flask, to it few ml of methanol was added to dissolve the drug completely. Then the volume was made up to the mark using distilled water.

### Calibration curve values for the estimation of efavirenz

Concentration[mcg/ml]	Absorbance*
2	0.112 $\pm$ 0.03
4	0.224 $\pm$ 0.02
6	0.336 $\pm$ 0.05
8	0.448 $\pm$ 0.1
10	0.56 $\pm$ 0.03

\*Values indicate Mean  $\pm$  S.D(n=3)



### Different formulations of drug and polymer

S.NO	Formulation	Drug : polymer
1	F1	Pure drug
2	F2	1:1 (Cil : $\beta$ CD)
3	F3	1:2 (Cil : $\beta$ CD)
4	F4	1:3 (Cil : $\beta$ CD)
5	F5	1:4 (Cil : $\beta$ CD)
6	F6	1:1 (Cil : HP- $\beta$ CD)
7	F7	1:2 (Cil : HP- $\beta$ CD)
8	F8	1:3 (Cil : HP- $\beta$ CD)
9	F9	1:4 (Cil : HP- $\beta$ CD)

### Preparation of Inclusion Complexes

The CDs used for the preparation of inclusion complexes were  $\beta$ -CD and HP- $\beta$ -CD. Efavirenz-CDs inclusion complexes were prepared in 1:1, molar ratio by using two different methods: (1) solvent method and compared with physical mixtures of efavirenz-CDs.

#### (a) Physical mixture

The physical mixtures were prepared by mixing pulverized powder of efavirenz with  $\beta$ -CD and HP  $\beta$ -CD mixture was prepared.

#### (b) Solvent evaporation method

Dissolve HP - $\beta$  CD and  $\beta$ - CD separately with Efavirenz in methanol and then evaporate the solvent under room temperature to produce a solid.

#### (c) Fluidised bed coating process

The solution was then sprayed through a nozzle onto the fluidized non-peril cores. The detailed operating conditions were as follows : inlet air temperature ,50 $^{\circ}\text{C}$  ; product temperature,32-35 $^{\circ}\text{C}$ ;air flow rate,97-103 $\text{m}^3/\text{h}$ ; spray rate,1.0 ml/min; atomizing pressure,1.5-1.6 bar; spray nozzle diameter,0.5mm.After drug/carrier layering, the pellets were dried for a further 15 min at 35 $^{\circ}\text{C}$  in a coating chamber. Batch size, calculated on the basis of

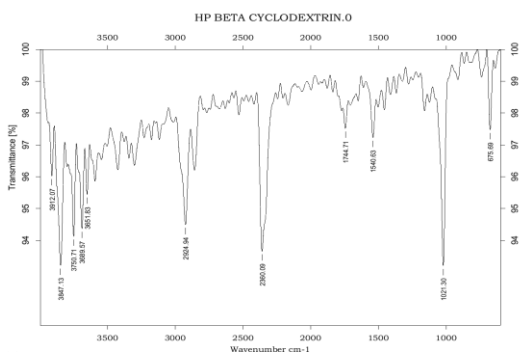
non-peril cores, was 50 g. Pellets were gathered and stored in sealed containers until analysis.

**Results and discussion**

**FTIR Spectroscopy**



**Fig 02: FTIR spectrum for the efavirenz and cyclodextrin mixture**



**Fig 03: FTIR spectrum for the cyclodextrin Assay of prepared complex:**

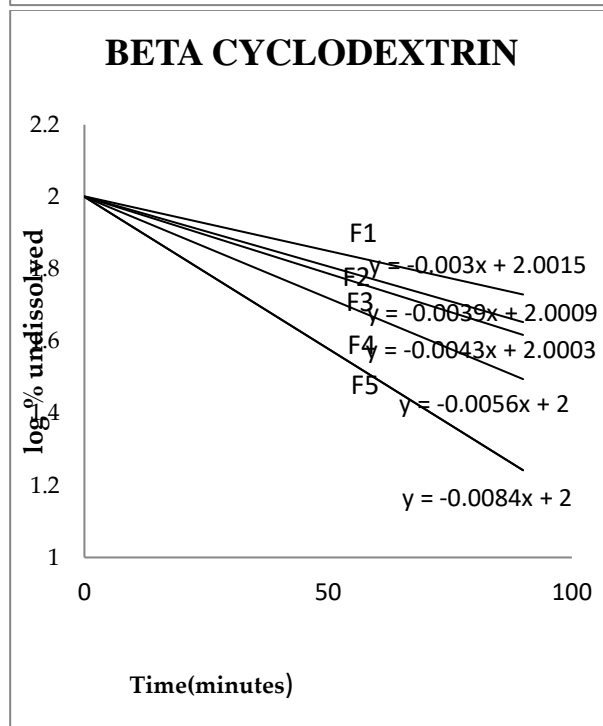
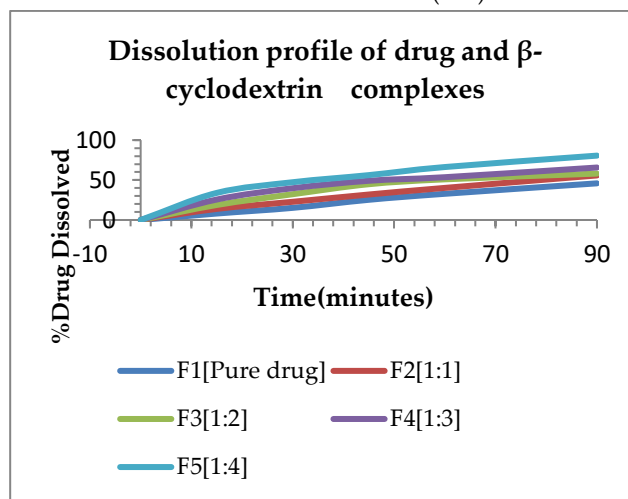
**Dissolution studies:**

The dissolution studies were conducted using a LA-BINDIA dissolution tester based on Pharmacopoeia Method II [Paddle method]. Samples containing 100mg of efavirenz were placed on a bowl and immersed in 900ml of 0.3% SLS solution thermostatically maintained at 37±0.5°C at a rotation rate of 75 rpm at appropriate time intervals, 5ml of the sample was withdrawn and replaced in order to maintain sink conditions and filtered. The filtrate was analysed by UV for estimation of efavirenz.

**Dissolution rate test profile of drug and β-cyclodextrin complexes:**

S. No	Time	%Drug dissolved*				
		Pure drug	F1 [1:1]	F2 [1:2]	F3 [1:3]	F4 [1:4]
1	15	8.1±0.01	13.9±0.02	18.8±0.6	25.6±0.06	33.9±0.04
2	30	15.2±0.05	22.8±0.08	32.3±0.05	39.8±0.03	47.3±0.09
3	45	25.3±0.07	31.9±0.03	44.8±0.08	49.1±0.05	56.2±0.05
4	60	32.8±0.04	40.2±0.02	50.9±0.12	53.6±0.02	68.9±0.03
5	90	45.9±0.1	55.8±0.07	58.1±0.01	65.7±0.09	80.6±0.02

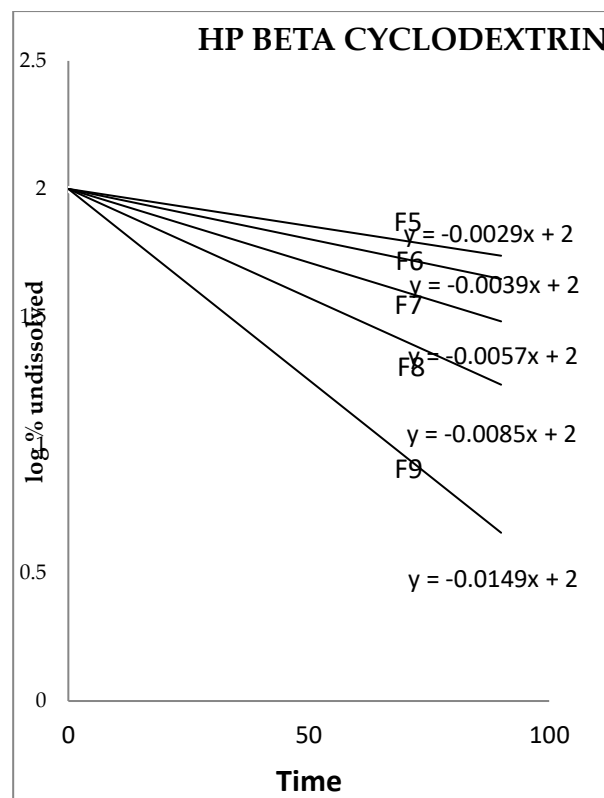
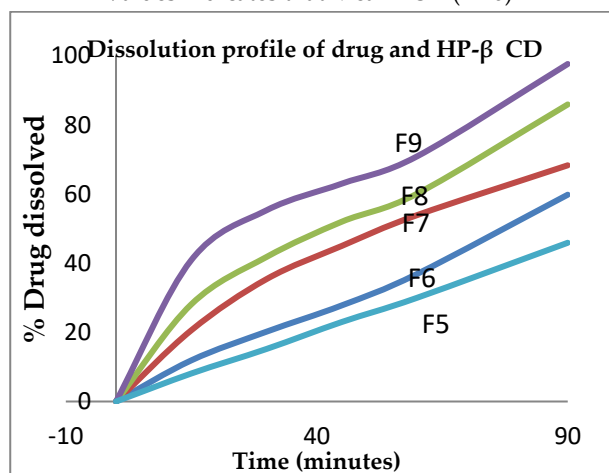
\*Values indicate Mean± SD (n=6)



### Dissolution rate test profile of drug and HP- $\beta$ cyclodextrin:

S. N O	Time	%Drug dissolved*				
		Pure drug F5	F6 [ 1:1]	F7 [1:2]	F8 [ 1:3]	F9 [1:4]
1	15	8.1±0.01	11.9±0.04	20.6±0.02	28±0.03	40.9±0.03
2	30	15.2±0.05	20.2±0.02	35.4±0.09	41.8±0.08	55.3±0.05
3	45	25.3±0.07	27.8±0.07	47.2±0.04	51.6±0.01	63.9±0.08
4	60	32.8±0.04	36.9±0.03	53.9±0.03	60.1±0.03	70.9±0.01
5	90	45.9±0.1	59.8±0.1	68.3±0.05	85.9±0.05	97.6±0.1

\*Values indicates that Mean  $\pm$  SD (n =6)



### Conclusion

Complexes have been successfully prepared by deposition of the co-precipitates of Efavirenz /HP- $\beta$  CD done on non-peril pellets using a fluid -bed coating technique. The dissolution of the HP- $\beta$  CD/Cil solid dispersions was enhanced greatly at HP- $\beta$  CD /Cil ratios of over 4/1 and a coating weight gain of about 100%. It is indicated that the fluid bed coating technique can possibly be used to deposit solid dispersions on non-perils and may find application in the manufacturing and scaling-up of solid dispersion formulations in the future. So that F9 formulation shows enhanced solubility, in order to increase the bioavailability of efavirenz.

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