OPTIMIZATION OF EFAVIRENZ TABLET FORMULATION
EMPLOYING β CD AND SOLUPLUS BY 2² FACTORIAL DESIGN

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ABSTRACT
Efavirenz, a widely prescribed antiretroviral drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It needs enhancement in the dissolution rate in its formulation development. Complexation with β-cyclodextrin (βCD) and use of surfactant (Soluplus) are tried for enhancing the dissolution rate of efavirenz in its formulation development. The objective of the present study is optimization of efavirenz tablet formulation employing βCD and Soluplus by 2² factorial design. Formulation of efavirenz tablets with NLT 85% dissolution in 15 min employing βCD and Soluplus was optimized by 2² factorial design. Four efavirenz (50 mg) tablet formulations were prepared using selected combinations of the two factors as per 2² factorial design. Efavirenz tablets were prepared by direct compression method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. All the efavirenz tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets. Much variations were observed in the disintegration and dissolution characteristics of the efavirenz tablets prepared due to formulation variables. The disintegration times were in the range 25 sec to 6 min 30 sec with various tablets. Efavirenz tablets (Eb) which are prepared employing βCD in 1:0.5 ratio of drug: βCD and Soluplus at 2 % of drug content gave very rapid dissolution of efavirenz than others. These tablets (Eb) gave 99.65 % dissolution in 15 min. The increasing order of dissolution rate (K₁) observed with various formulations was Eb>E₁b > Ea > E₁. For optimization, percent drug dissolved in 15 min was

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taken as response (Y) and level of βCD as (X_1) and level of Soluplus as (X_2). The polynomial equation describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data was found to be 

\[ Y = 69.88 + 8.68 \, (X_1) + 24.9 \, (X_2) - 13.56 \, (X_1 \, X_2). \]

Based on the above polynomial equation, the optimized efavirenz tablet formulation with NLT 85% dissolution in 15 min could be formulated employing βCD at 1:2.75 ratio of drug: βCD and Soluplus at 1.64 % of drug content. The optimized efavirenz (50 mg) tablet formulation prepared employing βCD (137.5 mg / tablet) and Soluplus (0.82 mg / tablet) gave 85.69% dissolution in 15 min fulfilling the target dissolution set. Thus optimization by 2^2 factorial design could be successfully used for the development of efavirenz tablets with NLT 85 % dissolution in 15 min

**KEYWORDS:** Efavirenz tablets, Optimization, β-cyclodextrin, Soluplus, Factorial Design.

**INTRODUCTION**

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process. Efavirenz, a widely prescribed antiretroviral drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development.

Several techniques\(^1\) such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches complexation with cyclodextrins and use of surfactants have gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected.\(^2,3\) Cyclodextrins have been receiving increasing application in
pharmaceutical formulation in recent years due to their approval by various regulatory agencies.\[^{4,5}\] Soluplus is polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft co- polymer. Soluplus increased the solubility and enhanced the bioavailability of actives in solid solutions. Itraconazole and fenofibrate showed significant increase in the bioavailability with Soluplus.\[^{6}\] The solubility and dissolution rate of valsartan was effectively enhanced by using Soluplus in the form of solid dispersions.\[^{7}\]

Complexation with β-cyclodextrin (βCD) and use of Soluplus (a non-ionic surfactant) are tried for enhancing the dissolution rate of efavirenz in its formulation development. The objective of the present study is optimization of efavirenz tablet formulation employing βCD and Soluplus by $2^2$ factorial design. Formulation of efavirenz tablets with NLT 85% dissolution in 15 min employing βCD and Soluplus was optimized by $2^2$ factorial design.

Optimization\[^{8}\] of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy. In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality. The objective of the present study is optimization of efavirenz tablet formulation employing βCD and Soluplus by $2^2$ factorial design.

**EXPERIMENTAL**

**MATERIALS**

Efavirenz was a gift sample from M/s. Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatnam. β Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Soluplus was a gift sample from BASF, the chemical company, Hyderabad. All other materials used were of pharmacopoeial grade.
METHOADS

Estimation of Efavirenz

A UV Spectrophotometric method based on the measurement of absorbance at 245 nm in water containing 2% Sodium lauryl sulphate (SLS) was used for the estimation of efavirenz. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer’s law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85% and 1.20% respectively. No interference by the excipients used in the study was observed.

Formulation of Efavirenz Tablets

For optimization of efavirenz tablets as per $2^2$ factorial design, the βCD and Soluplus are considered as the two factors. The two levels of the factor A (βCD) are 1:0.5 and 1:5 ratio of drug: βCD and the two levels of the factor B (Soluplus) are 0.2% and 2% of drug content. Four efavirenz tablet formulations employing selected combinations of the two factors i.e. βCD and Soluplus as per $2^2$ factorial design were formulated and prepared by direct compression method.

Preparation of Efavirenz Tablets

Efavirenz (50 mg) tablets were prepared by direct compression method as per the formula given in Table 1.

Efavirenz - βCD - Soluplus inclusion complexes involved in the formulation of efavirenz tablets were initially prepared by kneading method. Efavirenz, βCD and Soluplus were triturated in a mortar with a small volume of solvent consisting of a blend of dichloromethane: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120. The solid inclusion complexes prepared and all other ingredients as per the formula in each case were blended in a closed polyethylene bag and were compressed into tablets using an 8- station RIMEK tablet punching machine employing 9 mm or 12 mm round and flat punches to a hardness of 4-6 kg/cm². In each case 100 tablets were compressed.

Evaluation of Tablets

All the efavirenz tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows.
HARDNESS
The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm².

Friability
The friability of the tablets was measured in a Roche friabilator using the formula:
Friability (%) = [(Initial weight - Final weight) / (Initial weight)] x 100

Drug Content
Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of efavirenz was taken into 100 ml volumetric flask, dissolved in water containing 2 % SLS and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with water containing 2 % SLS and assayed for efavirenz at 245 nm.

Disintegration time
Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study
Dissolution rate of efavirenz tablets prepared was studied in water containing 2 % SLS (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for efavirenz at 245 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data
The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE₃₀) values were estimated as suggested by Khan.\[9\]

RESULTS AND DISCUSSION
The objective of the present study is to optimize the efavirenz tablet formulation employing βCD and Soluplus by 2² factorial design to achieve NLT 85% dissolution in 15 min.
According to BCS guidance of USFDA and WHO\cite{10-11}, a drug product is considered to be very rapidly dissolving when not less than 85% of the labelled amount of the drug dissolved in 15 min at the three physiological pH’s of 1.2, 4.5 and 6.8. Hence target dissolution to be achieved is fixed at NLT 85% dissolution in 15 min in the formulation development of efavirenz tablets.

For optimization of efavirenz tablets as per $2^2$ factorial design the βCD and Soluplus are considered as the two factors. The two levels of the factor A (βCD) are 1: 0.5 and 1:5 ratio of drug: βCD and the two levels of the factor B (Soluplus) are 0.2% and 2.0% of drug content. Four efavirenz tablet formulations employing selected combinations of the two factors i.e. βCD and Soluplus as per $2^2$ factorial design were formulated and prepared by direct compression method as per the formulae given in Table 1. The efavirenz tablets prepared were evaluated for various physical parameters and dissolution rate characteristics.

The physical parameters of the efavirenz tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.0-5.0 kg/cm$^2$. Weight loss in the friability test was less than 0.85% in all the cases. Efavirenz content of the tablets prepared was within 100±3%. Much variations were observed in the disintegration and dissolution characteristics of the efavirenz tablets prepared. The disintegration times were in the range 25 sec to 6 min 30 sec. All the efavirenz tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets.

Dissolution rate of efavirenz tablets prepared was studied in water containing 2% SLS. The dissolution profiles of the tablets are shown in Fig. 1 and the dissolution parameters are given in Table 3. Dissolution of efavirenz from all the tablets prepared followed first order kinetics with coefficient of determination ($R^2$) values above 0.954. The first order dissolution rate constant ($K_1$) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate ($K_1$) and $D_{30}$ values of the tablets prepared due to formulation variables.

Efavirenz tablets (Eb) which are prepared employing βCD in 1:0.5 ratio of drug: βCD and Soluplus at 2% of drug content gave very rapid dissolution of efavirenz than others. These tablets (Eb) gave 99.65% dissolution in 15 min. The increasing order of dissolution rate ($K_1$) observed with various formulations was Eb>Eab > Ea > E1.
For optimization, percent drug dissolved in 15 min was taken as response (Y) and level of βCD as (X₁) and level of Soluplus as (X₂). The polynomial equation describing the relationship between the response, Y and the variables, X₁ and X₂ based on the observed data was found to be \( Y = 69.88 + 8.68X_1 + 24.9X_2 - 13.56X_1X_2 \). Based on the above polynomial equation, the optimized efavirenz tablet formulation with NLT 85% dissolution in 15 min could be formulated employing βCD at 1:2.75 ratio of drug: βCD and Soluplus at 1.64 % of drug content. To verify efavirenz tablets were formulated employing the optimized levels of βCD and Soluplus. The formula of the optimized efavirenz tablets is given in Table 1. The optimized efavirenz tablet formulation was prepared by direct compression method and the tablets were evaluated. The physical parameters of the optimized formulation are given in Table 2 and dissolution parameters are given in Table 3. The hardness of the optimized efavirenz tablets was 4.5 kg/sq.cm. Friability (percent weight loss) was less than 0.85 %. Disintegration time of the tablets was in the range 20-25 sec. The optimized efavirenz tablet formulation gave 85.69% dissolution in 15 min fulfilling the target dissolution set.

Hence optimization by \( 2^2 \) factorial design could be successfully used for the development of efavirenz tablets with NLT 85 % dissolution in 15 min.

**Table 1: Formulae of Efavirenz Tablets Prepared as per \( 2^2 \) Factorial Design Employing βCD and Soluplus and Optimized Formulation**

<table>
<thead>
<tr>
<th>Ingredient (mg/tab)</th>
<th>( E_1 )</th>
<th>( E_a )</th>
<th>( E_b )</th>
<th>( E_{ab} )</th>
<th>( E_{opt} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>βCD</td>
<td>25</td>
<td>250</td>
<td>25</td>
<td>250</td>
<td>137.5</td>
</tr>
<tr>
<td>Soluplus</td>
<td>0.1</td>
<td>0.1</td>
<td>1.0</td>
<td>1.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>9.2</td>
<td>14</td>
<td>9.2</td>
<td>14</td>
<td>9.2</td>
</tr>
<tr>
<td>Talc</td>
<td>2.3</td>
<td>3.5</td>
<td>2.3</td>
<td>3.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.3</td>
<td>3.5</td>
<td>2.3</td>
<td>3.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Aerosil</td>
<td>1.15</td>
<td>1.75</td>
<td>1.15</td>
<td>1.75</td>
<td>1.15</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>139.95</td>
<td>27.15</td>
<td>139.05</td>
<td>26.25</td>
<td>26.73</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>230</td>
<td>350</td>
<td>230</td>
<td>350</td>
<td>230</td>
</tr>
</tbody>
</table>

**Table 2: Physical Parameters of Efavirenz Tablets Prepared as per \( 2^2 \) Factorial Design Employing βCD and Soluplus and Optimized Formulation**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (% Wt loss)</th>
<th>Disintegration Time (min-sec)</th>
<th>Drug Content (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_1 )</td>
<td>5.0</td>
<td>0.85</td>
<td>0-25</td>
<td>98.2</td>
</tr>
<tr>
<td>( E_a )</td>
<td>5.0</td>
<td>0.80</td>
<td>0-30</td>
<td>99.9</td>
</tr>
<tr>
<td>( E_b )</td>
<td>4.0</td>
<td>0.65</td>
<td>0-55</td>
<td>98.3</td>
</tr>
<tr>
<td>( E_{ab} )</td>
<td>4.0</td>
<td>0.70</td>
<td>0-40</td>
<td>98.9</td>
</tr>
<tr>
<td>( E_{opt} )</td>
<td>4.5</td>
<td>0.85</td>
<td>0-25</td>
<td>99.7</td>
</tr>
</tbody>
</table>
Table 3: Dissolution Parameters of Efavirenz Tablets Prepared as per $2^2$ Factorial Design Employing βCD and Soluplus and Optimized Formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PD$_{15}$ (%)</th>
<th>DE$_{30}$ (%)</th>
<th>$K_1 \times 10^2$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_1$</td>
<td>22.70</td>
<td>22.76</td>
<td>2.46</td>
</tr>
<tr>
<td>$E_a$</td>
<td>67.20</td>
<td>57.38</td>
<td>6.17</td>
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<tr>
<td>$E_b$</td>
<td>99.65</td>
<td>88.76</td>
<td>45.7</td>
</tr>
<tr>
<td>$E_{ab}$</td>
<td>88.92</td>
<td>80.95</td>
<td>9.56</td>
</tr>
<tr>
<td>$E_{opt}$</td>
<td>85.69</td>
<td>77.76</td>
<td>8.95</td>
</tr>
</tbody>
</table>

Fig.1: Dissolution Profiles of Efavirenz Tablets Prepared Employing βCD and Soluplus as per $2^2$ Factorial Design and Optimized Formulation

CONCLUSIONS

1. All the efavirenz tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets.
2. Much variations were observed in the disintegration and dissolution characteristics of the efavirenz tablets prepared due to formulation variables.
3. The disintegration times were in the range 25 sec to 6 min 30 sec with various tablets.
4. Efavirenz tablets ($E_b$) which are prepared employing βCD in 1:0.5 ratio of drug: βCD and Soluplus at 2% of drug content gave very rapid dissolution of efavirenz than others. These tablets ($E_b$) gave 99.65% dissolution in 15 min.
5. The increasing order of dissolution rate ($K_1$) observed with various formulations was $E_b > E_{ab} > E_a > E_1$.
6. For optimization, percent drug dissolved in 15 min was taken as response ($Y$) and level of βCD as ($X_1$) and level of Soluplus as ($X_2$). The polynomial equation describing the relationship between the response, $Y$ and the variables, $X_1$ and $X_2$ based on the observed data was found to be $Y = 69.88 + 8.68 \times X_1 + 24.9 \times X_2 - 13.56 \times X_1 \times X_2$. 
7. Based on the above polynomial equation, the optimized efavirenz tablet formulation with NLT 85% dissolution in 15 min could be formulated employing βCD at 1:2.75 ratio of drug: βCD and Soluplus at 1.64 % of drug content.

8. The optimized efavirenz (50 mg) tablet formulation prepared employing βCD (137.5 mg / tablet) and Soluplus (0.82 mg/ tablet) gave 85.69% dissolution in 15 min fulfilling the target dissolution set.

9. Thus optimization by $2^2$ factorial design could be successfully used for the development of efavirenz tablets with NLT 85 % dissolution in 15 min.

REFERENCES


