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**Research Article**

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# Experimental deign as an approach for design and optimize the efavirenz oral disintegrating tablets

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**ABSTRACT**

*Oral route of drug administration is the most common and preferred route of administration. Oral dispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Efavirenz which is an oral nucleoside reverse transcriptase inhibitor (NRTI) of human immunodeficiency virus. The project was aimed to enhance the solubility which intern improves the bioavailability. DESIGN EXPERT version 8.0.7.1 was selected for designing of the present project to make the project economical and statically significant. Superdisintegrates (croscarmellose sodium, sodium starch glycolate) used in different concentrations. Prepared tablets were evaluated for various in-vitro evaluation tests such as weight variation, thickness, wetting time, drug content, in-vitro disintegration time, in-vitro dissolution. The formulations are analyzed for considered response i.e. disintegration, dissolution with the help of DESIGN EXPERT software and the based on the considered responses an optimized formulation was developed. The optimized formulation developed showed the in-vitro drug release greater than 80% within 30min and 96.67± 1.18 withi n 60min.*

**Key words:** Efavirenz, Superdisintegrants, Design Expert, Oral Disintigrating tablets

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## INTRODUCTION

European pharmacopoeia also adopted the term “Orodispersible tablet” as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing, despite various terminologies used [1]. Oral delivery continues to be the most popular route of administration due to its versatility, ease of administration and probably most importantly patient compliance Providing patients with simplified, convenient oral medications that improve compliance and thus result in more effective treatment has been one of the major drivers of innovation in the oral drug delivery market. Oro dispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue [2]. Orodispersible tablets are also known as Mouth dissolving tablet, Oral disintegrating tablets, Fast dissolving drug deliver, Rapidmelts tablet, Porous tablet, Quick dissolving tablets etc [3]. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia and Centre for Drug Evaluation and Research (CDER) [4-7].

Recently, European Pharmacopoeia has used the term orodispersible tablets [8]. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within three minutes before swallowing [9]. United States Pharmacopoeia has also approved these dosage forms as orodispersible tablets [10-12]. Thus,

Orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. It is ease of administration in the population especially for pediatric, geriatric, or any mentally retarded person makes it a very popular dosage form [13]. Due to the presence of super disintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action [14]. Since the absorption is taking place directly from the mouth, bioavailability of the drug increases [15]. Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its numerous advantages.

## EXPERIMENTAL SECTION

### Materials

Efavirenz and Croscarmellose sodium was a Gift sample from Hetero drugs Pvt Ltd, (Hyderabad). The diluents used are Sodiumstarch glycolate and sodium lauryl sulphate Yarrow chem products,(Mumbai). Microcrystalline cellulose and menthol from Simla industries, (Mumbai).The Lubricants are Magnesium stearate and Talc S.D.Fine chemicals,(Mumbai).The other are Sodium hydroxide from Qualigens finechemicals,(Mumbai).

### Experimental Design

Response Surface methodology was implanted to study the effect of formulation variables in the development of Oral disintegrating tablets of Efavirenz. Response surface designs are more effective in minimize defects and maximize yield [16]. In the present investigation two independent formulation variables X1: Cross caramellose sodium, X2: Sodium starch glycolate, Response variables tested include Y1: Disintegration time, Y2: %CDR in Dissolution. Box – Behnken Design is a class of second – order designs based on three – level incomplete factorial designs. This model has the quadratic form containing linear terms for all factors, squared terms for all factors and products of all pairs of factors.

$$\gamma = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$$

**Table 1. Composition of superdisintegrants**

| | CCS | SSG |
|---|---|---|
| Low | 0.75mg | 3mg |
| Intermediate | 4.5mg | 7.5mg |
| High | 7.5mg | 12mg |

**Table 2. Formulation Design**

| RUNS | CCS | SSG |
|---|---|---|
| 1 | 7.5 | 7.5 |
| 2 | 4.5 | 12 |
| 3 | 4.5 | 7.5 |
| 4 | 0.75 | 3 |
| 5 | 0.75 | 7.5 |
| 6 | 7.5 | 12 |
| 7 | 7.5 | 3 |
| 8 | 0.75 | 12 |
| 9 | 4.5 | 3 |
| 10 | 0.75 | 3 |
| 11 | 0.75 | 7.5 |
| 12 | 4.5 | 3 |

### Preparation of Efavirenz Tablets

Oral disintegrating tablets of Efavirenz was prepared by direct compression Efavirenz and Superdisintegrants (Cross caramellose sodium, Sodium starch glycolate) and, filler (MCC), solubilizer (SLS), lubricant (Magnesium stearate), glidant (Talc) were blended together by dry mixing in a laboratory mixer (polybag) for 10 mins. The mixture was compressed by using 8mm standard flat round punch and die set at compression force 3-4ton. The super disintegrants were selected by taking low, intermediate and high concentration [17].

**Table 3. Composition of Efavirenz Oral disintegrating tablets**

| Ingredients | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 | F-9 | F-10 | F-11 | F-12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Efavirenz | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Croscaramellose sodium | 7.5 | 4.5 | 4.5 | 0.75 | 0.75 | 7.5 | 7.5 | 0.75 | 4.5 | 0.75 | 0.75 | 4.5 |
| Sodium starch glycolate | 7.5 | 12 | 7.5 | 3 | 7.5 | 12 | 3 | 12 | 3 | 3 | 7.5 | 3 |
| Micro crystalline cellulose | 125 | 123.5 | 128 | 136.25 | 131.75 | 120.5 | 129.5 | 127.5 | 132.5 | 136.25 | 131.75 | 132.5 |
| Sodium lauryl sulphate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Tablet weight | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

**Drug- excipient compatibility studies by FTIR & DSC**

Compatibility studies were performed using FTIR spectrophotometer and Differential scanning calorimetry analysis was performed for detecting drug-polymer interaction. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc technique using Brooker FTIR. For thermal analysis of drug and drug-excipient mixtures, a differential scanning calorimeter using Mettler Toledo DSC 823e. Individual samples (drug and excipients) as well as mixtures of drug and selected excipients were taken in the pierced DSC aluminum pan and scanned in the temperature range of 25–300 °C (at the heating rate of 10 °C $min^{-1}$) under an atmosphere of dry nitrogen [16,17].

**Micrometric Properties**

**Angle of repose:**

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [18].

$$\tan\theta = \frac{h}{r}$$

**Bulk density**

Bulk density includes the contribution of interparticulate void volume weighed quantity of the powder sample passed into 50 ml graduated cylinder. The powder sample was carefully leveled in the cylinder without compacting. The unsettled apparent volume was read to the nearest graduated unit and noted. The bulk density was calculated by using the formula [18].

Bulk density= (Weight of powder blend)/(Bulk Volme)

**Tapped density**

Tapped density was calculated using the following equation [18].

Tapped density = (Weight of the powder blend)/ (Tapped volume)

**Hausner's Ratio:**

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density [19].

Hausner's ratio = (Tapped density)/ (Bulk density)

**Compressibility index (Carr's Index)**

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property [19].

$$\text{Cars index} = \frac{\text{Tapped density-Bulk density}) \times 100}{\text{Tapped density}}$$

**Post Compression Evaluation**

**Average Weight**

The weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit [18].

**Wetting time**

The method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water, a tablet was put on the paper, and the time for complete wetting was measured [20].

***In- vitro* Disintegration Test**

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 phosphate buffer maintained at 37 ±2 $^{\circ}$C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 phosphate buffer [20]. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

**Thickness**

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using vernier calipers [18].

**Hardness**

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness[18]. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm$^2$.

**Friability**

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded [18].

**Content Uniformity**

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg of drug was weighed accurately and dissolved in 100ml of methanol. The solution was shaken thoroughly. Then transfer 1mL of above solution into 100mL volumetric flask and make up the volume with methanol and then further diluted to get the absorbance. The absorbance of the diluted solutions was measured at 246nm. The concentration of the drug was computed from the standard curve of the Efavirenz in methanol [21].

***In-Vitro* Dissolution studies**

*In-vitro* dissolution study of Efavirenz tablets was carried using Lab india DS 5000 dissolution test apparatus[20]. The details are given as below. Tablet was introduced into dissolution test apparatus and the apparatus was set at 50rpm motion. 10 ml of sample was withdrawn for 5min, 10min, 15min, 30min, 45min, 60min up to 1 hr. Samples withdrawn were analyzed by UV spectrophotometer at 246nm using at 370C ± 0.50C using 6.8pH buffer as blank.

**Optimization:**

The responses of the 12 formulations ie., Disintegration time and Dissolution were entered in the Design expert and further obtained the optimized formulation design which is as below

**Table 4. Composition of Formulations based on Resposive Surface Design with observed responses**

| Std | RUN | Factor1 CCS | Factor 2 SSG | Disintegration Sec | Dissolution % |
|---|---|---|---|---|---|
| **5** | **1** | 7.50 | 7.5 | 45 | 84.34 |
| **3** | **2** | 4.5 | 12 | 41 | 88.25 |
| **6** | **3** | 4.5 | 7.5 | 49 | 91.24 |
| **2** | **4** | 0.75 | 3 | 93 | 67.04 |
| **9** | **5** | 0.75 | 7.5 | 52 | 83.25 |
| **4** | **6** | 7.5 | 12 | 26 | 91.85 |
| **7** | **7** | 7.5 | 3 | 53 | 90.28 |
| **11** | **8** | 0.75 | 12 | 56 | 90.88 |
| **10** | **9** | 4.5 | 3 | 38 | 79.71 |
| **8** | **10** | 0.75 | 3 | 93 | 67.04 |
| **12** | **11** | 0.75 | 7.5 | 52 | 83.25 |
| **1** | **12** | 4.5 | 3 | 38 | 79.71 |

## RESULTS AND DISCUSSION

**Drug- excipient compatibility studies by FTIR & DSC**

FTIR spectrum of pure drug and physical mixture of drug and polymers were studied. Drug: polymer compatibility studies are very important in order to confirm the drug structure, its activity, and its degradation rate and release pattern with various polymeric substances used in the formulation. The characteristic absorption peaks of Efavirenz were obtained at wave numbers 3319.02 $cm^{-1}$, 2250.16$cm^{-1}$, 1749.37$cm^{-1}$, 1601.72$cm^{-1}$. Efavirenz with mixture of different polymers showed no considerable changes and there is no interaction between drug-polymer combination. The FTIR spectrograms were shown in the Figures.1-4. The DSC thermo gram study for drug and its formulations is also utilized for establishing physical characteristics. The DSC thermo gram of pure drug gave sharp endothermic peak at temperature 131.26$^0$C, which indicates its melting point. The DSC thermo gram of the optimized formulation shows an endothermic drug peak at 136.24$^0$C indicates no interaction with excipients. Thermograms can be seen at figures 5-6. The comparative study of these two thermo grams, i.e. drug and formulation shows the endothermic peak corresponding to the melting point of the drug. There was no significant change in the position of peak and its intensity for the tablet formulations. Thus, DSC study showed no interaction between the drug and polymers during granulation process.

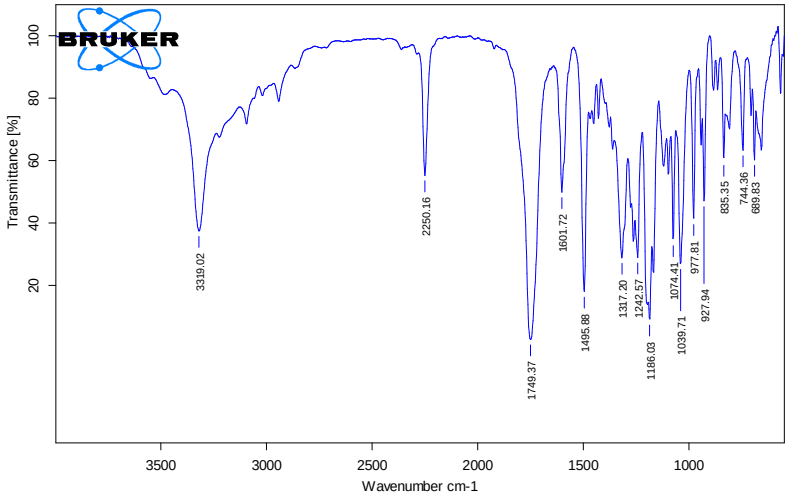



**Fig 1. FTIR spectra for Efavirenz**

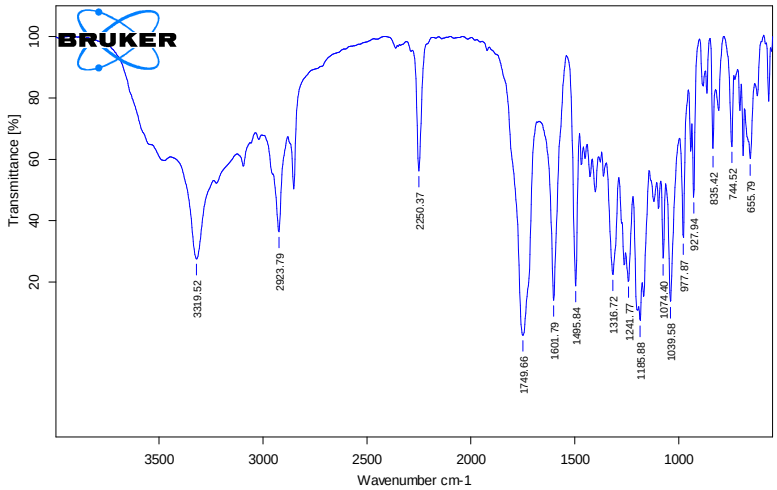



**Fig 2. FTIR spectra for Efavirenz with CCS**

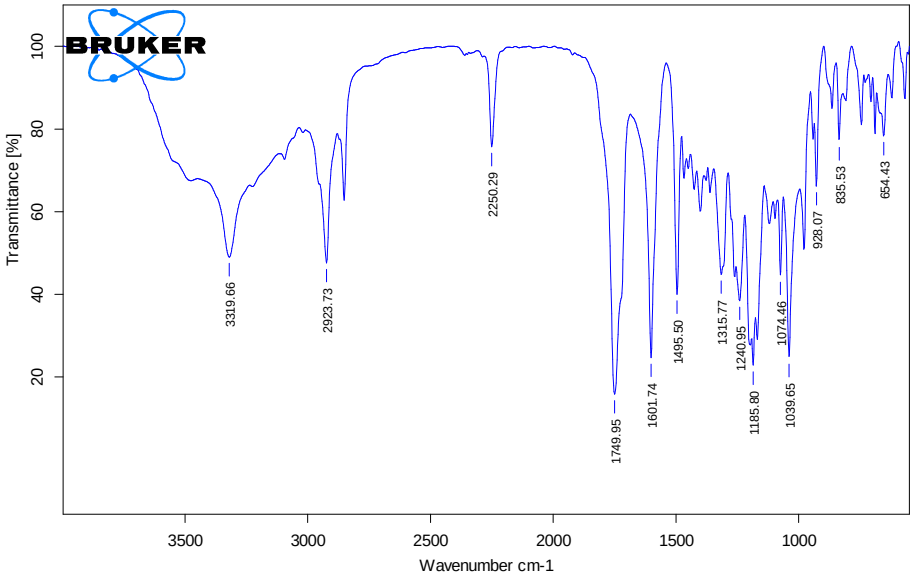



**Fig 3. FTIR spectra for Efavirenz+ Sodium Starch Glycolate**

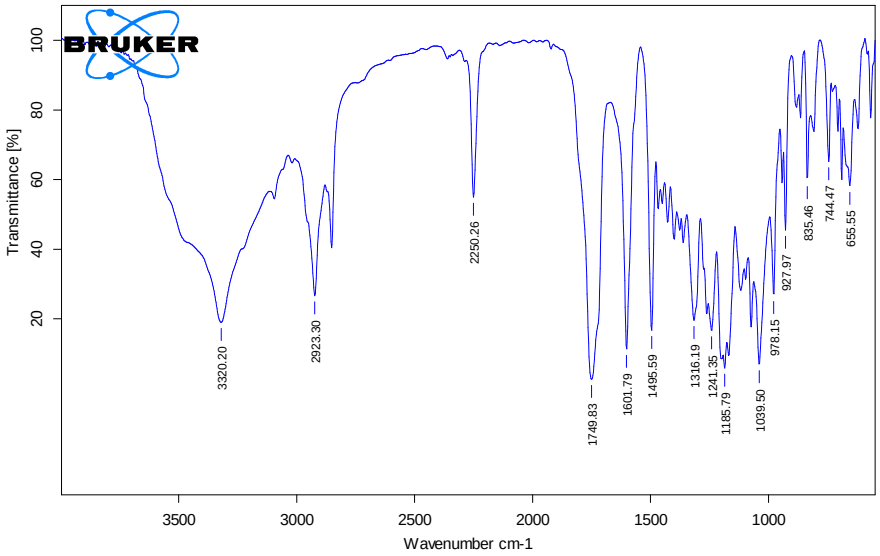



**Fig 4. FTIR spectra for Efavirenz + Microcrystalline Cellulose**

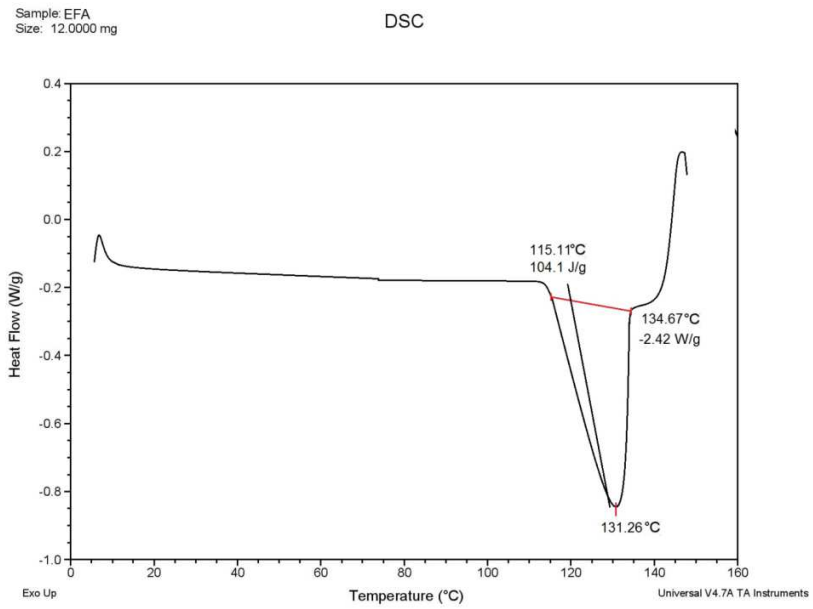



**Fig 5. DSC Spectra of Efavirenz**

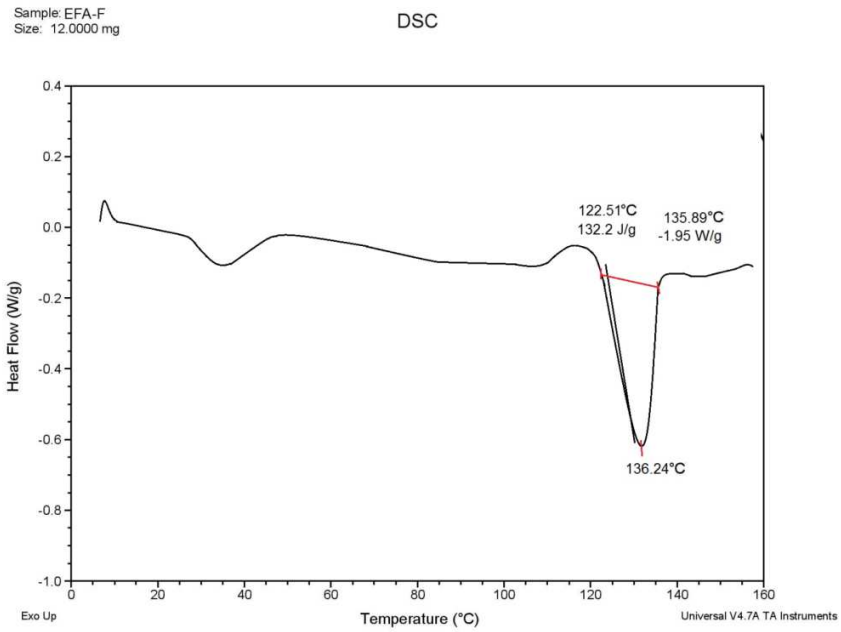



**Fig 6. DSC Spectra of Formulation**

**Micrometric Properties**

Precompression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include angle of repose, bulk density, tapped density, carr's index and haunser's ratio. The angle of repose for the formulations blend was carried out and the results were found to be in the range of $23^0$.94 - $30^0$.65 shows the angle of repose less than 30°, which reveals good flow property for compression into tablets. The mean bulk densities of the blend were found to be in the range from 0.246 to 0.319 g/ml. The mean tapped densities of powders were found to be in the range from 0.307 to 0.375 g/ml. Compressibility index was found in the range 10.64 to 19.64 which is less than 21% indicates better flow properties. Hausner's ratio was calculated for all the batches and it found 1.12 to 1.24 indicates better flow properties. The results were showed in table 5.

**Table 5. Results of Precompression parameters**

| Formulation code | Angle of repose Avg±SD (n=3) | Bulk Density (g/ml) Avg±SD (n=3) | Tapped Density (g/ml) Avg±SD (n=3) | Hausner's Ratio Avg±SD (n=3) | Compressibility Index (%) Avg±SD (n=3) |
|---|---|---|---|---|---|
| F-1 | 23°.94 ± 0.325 | 0.319±0.009 | 0.357±0.011 | 1.12±0.02 | 10.64±2.77 |
| F-2 | 25°.64 ± 0.826 | 0.294±0.014 | 0.334±0.018 | 1.13±0.05 | 11.72±4.55 |
| F-3 | 27°.15 ± 0.418 | 0.267±0.006 | 0.313±0.016 | 1.16±0.03 | 14.35±2.71 |
| F-4 | 30°.65 ± 0.488 | 0.246±0.014 | 0.307±0.023 | 1.24±0.01 | 19.64±1.22 |
| F-5 | 28°.65 ± 0.075 | 0.283±0.014 | 0.341±0.011 | 1.2±0.05 | 16.85±3.91 |
| F-6 | 25°.96 ± 0.870 | 0.278±0.012 | 0.319±0.009 | 1.14±0.02 | 12.97±2.30 |
| F-7 | 28°.96 ± 0.625 | 0.307±0.022 | 0.358±0.02 | 1.16±0.02 | 14.18±1.88 |
| F-8 | 27°.95 ± 0.637 | 0.294±0.014 | 0.349±0.011 | 1.18±0.03 | 15.63±2.27 |
| F-9 | 25°.29 ± 0.502 | 0.313±0.015 | 0.375±0.012 | 1.19±0.03 | 16.51±2.31 |

**Post Compression Evaluation**

The physical properties of tablets are shown in the Table 6. The hardness of the tablets was found to be in the range of 3 to 5 kg/cm$^2$. The friability of all the prepared tablets was found to be in the range of 0.68 to 0.91%, fulfilling the official requirement. The tablets of each formulation have shown acceptable uniformity of diameter and thickness was almost uniform in all the formulations and values ranged from 3.16mm to 3.56mm. The percentage drug content for all the formulation was found to be in a range of 93.83% to 103.75%. This ensures that it is within a limit according to IP specifications of 90-110% .The weight variation was found to be in the range of 249±7 to 250.5±6.68. This ensures that it is within a limit according to IP specifications of 7.5%. The results were showed in

table 6. When wetting time and *in-vitro* disintegration time were observed, they ranges from 46-61 sec and 26-93sec respectively and fulfilling the official requirements i.e, less than 1min. The results were showed in table 6.

**Table 6. Results of Postcompression parameters**

| Formulation code | Weight variation Avg±SD (n=20) | Thickness Avg±SD (n=3) | Hardness ($Kg/cm^2$) Avg ± SD (n=3) | Friability (%) | Drug content Avg ± SD (n=3) | Wetting time (min) | Disintegration time (min) |
|---|---|---|---|---|---|---|---|
| F1 | 249±7 | 3.26±0.01 | 3.33 ± 0.47 | 0.68 | 99.58±2.18 | 0.49 | 0.45 |
| F2 | 252±7.48 | 3.23±0.15 | 3 ± 0.81 | 0.81 | 101.66±1.04 | 0.54 | 0.41 |
| F3 | 250±7.07 | 3.26±0.11 | 4 ± 0.81 | 0.89 | 103.75±1.33 | 0.59 | 0.49 |
| F4 | 249±4.35 | 3.16±0.57 | 3.66 ± 0.94 | 0.78 | 92±0.54 | 0.53 | 1.33 |
| F5 | 252±6 | 3.56±0.10 | 3.66± 0.47 | 0.80 | 96±0.54 | 0.61 | 0.52 |
| F6 | 245.5±5.89 | 3.5±0.10 | 4 ± 0.81 | 0.66 | 100.33±0.71 | 0.46 | 0.26 |
| F7 | 250.5±6.68 | 3.16±0.05 | 3.66 ± 0.47 | 0.68 | 99.66±0.71 | 0.52 | 0.53 |
| F8 | 248±6.78 | 3.5±0.10 | 4.33 ± 0.47 | 0.91 | 93.83±1.5 | 0.55 | 0.56 |
| F9 | 250±7.07 | 3.26±0.11 | 3.33 ± 0.47 | 0.78 | 101.66±1.35 | 0.48 | 0.38 |

***In-Vitro* Dissolution studies**

The results of *in-Vitro* drug release data are given in figure 7-9. As per the results of dissolution studies by the end of 60mins the %cumulative drug release (CDR) was calculated, which ranges from 67.04 ± 1.28 to 91.85 ± 0.46. Formulation F4 Shows least CDR among all formulations i.e.67.04 and F6 has the maximum CDR 91.85. F6 has CCS and SSG in the range of 7.5 and 12 mg respectively where as F4 has 0.75 and 3 mg concentrations. From the above results it can be confirmed that at low levels CCS is having a positive effect on dissolution compared to high levels. SSG is having inverse effect at high levels it is a positive effect compared to low levels in combinations.

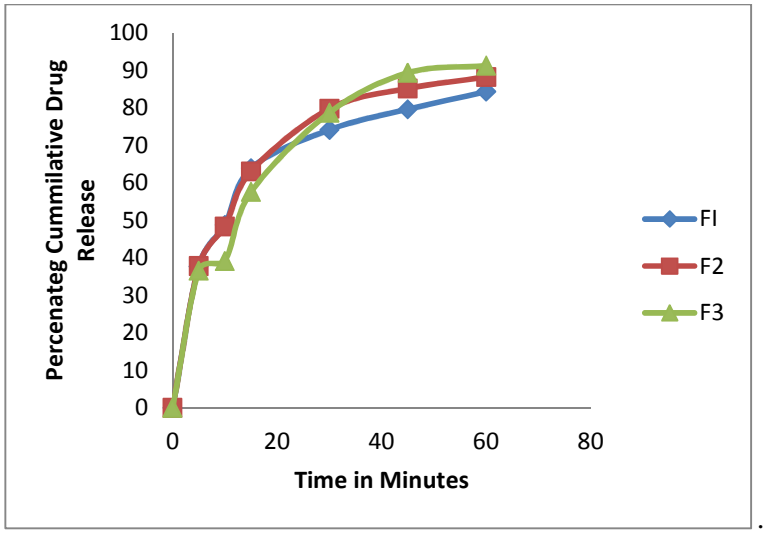



**Figure 7. *In-Vitro* drug release for formulation of F-1 to F-3**

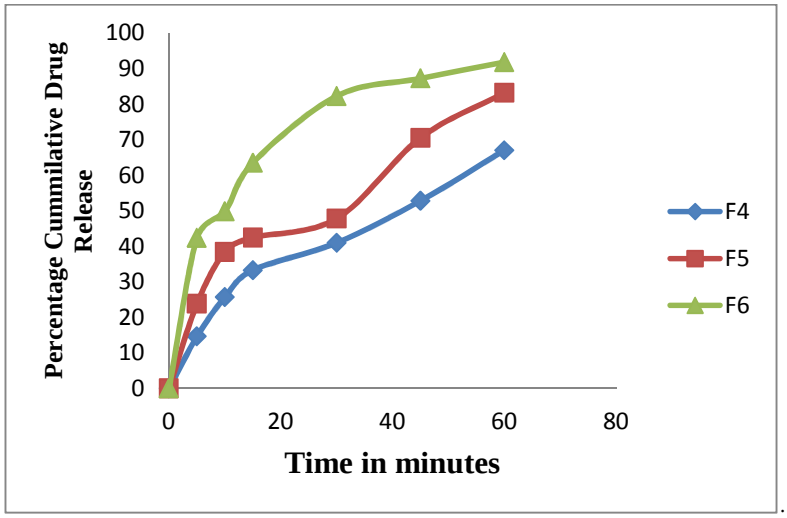



**Figure 8. *In-Vitro* drug release for formulation of F-4 to F-6**

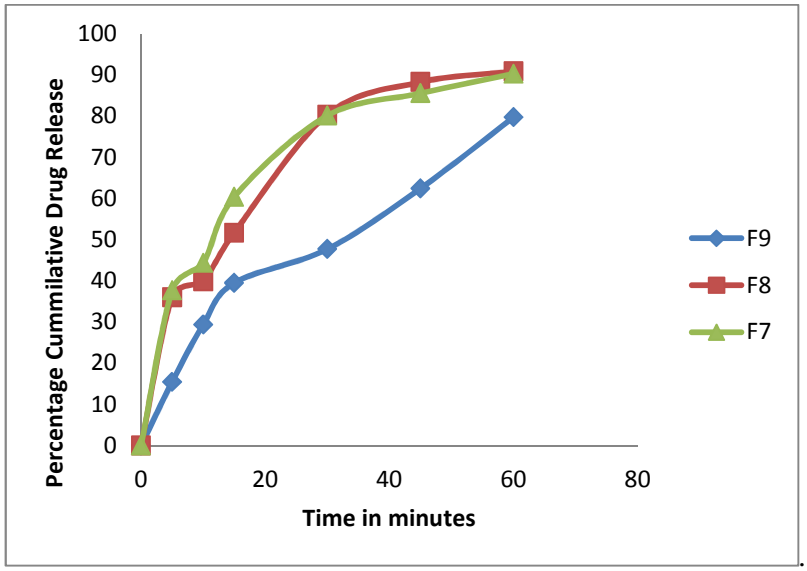



**Figure 9. *In-Vitro* drug release for formulation of F-7 to F-9**

**Resposive Surface analysis (Disintegration Time)**

Figure 10 and 11 represents the contour and three dimensional studies of response of disintegration properties of oral disintegrating tablets of Efavirenz. From the contour plot it can be concluded that SSG at higher levels has a completely greater influence in on responsive variables than CCS. From the contour graph it was observed that a decline in disintegration rate was observed with ascending concentrations of CCS. However a little positive effect was observed at intermediate levels in combination of CCS and SSG.

**Figure 10. Disintegration Contour Graph**

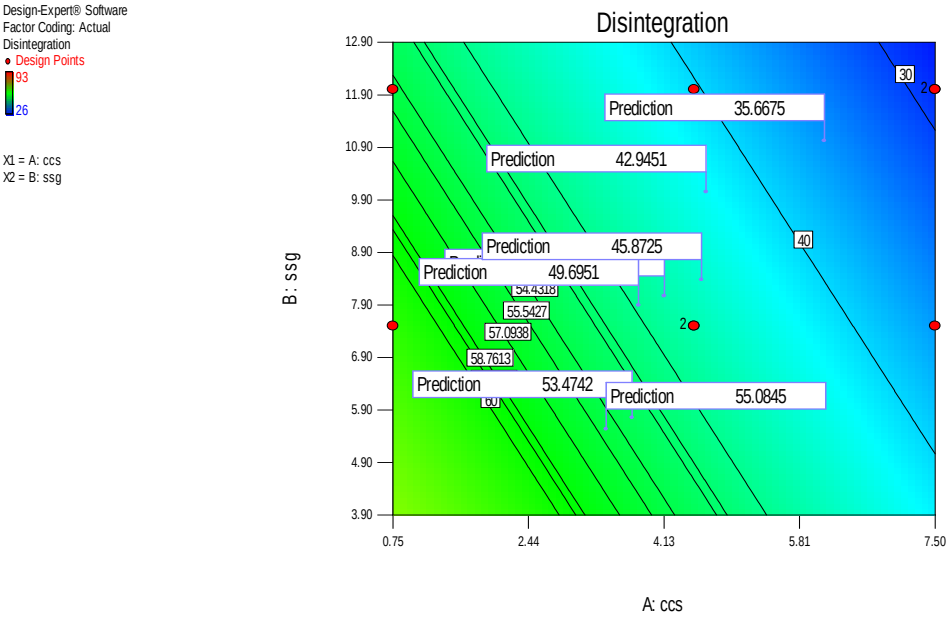
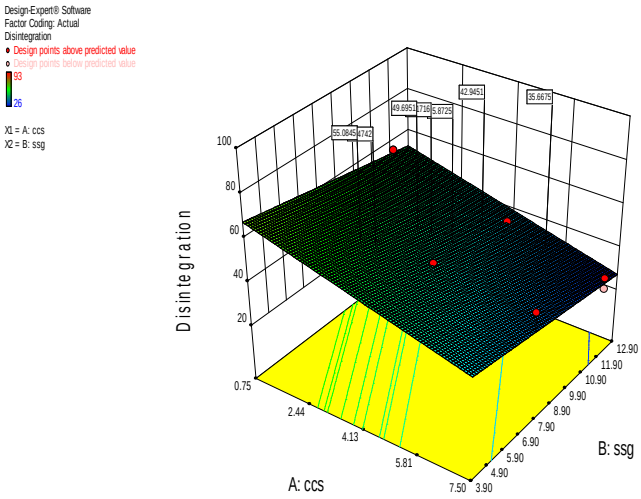



**Figure 11. Disintegration 3D Graph**




**Resposive Surface analysis ($t_{90\%}$)**

Figure 12 and 13 demonstrate the three dimensional response of 90% percentage of drug release of drug from oral disintegrating tablets of Efavirenz. From the graph it can be concluded that SSG at higher levels has a positive where as CCS has a inverse effect on dissolution.

**Figure 12. Dissolution Contour Graph**

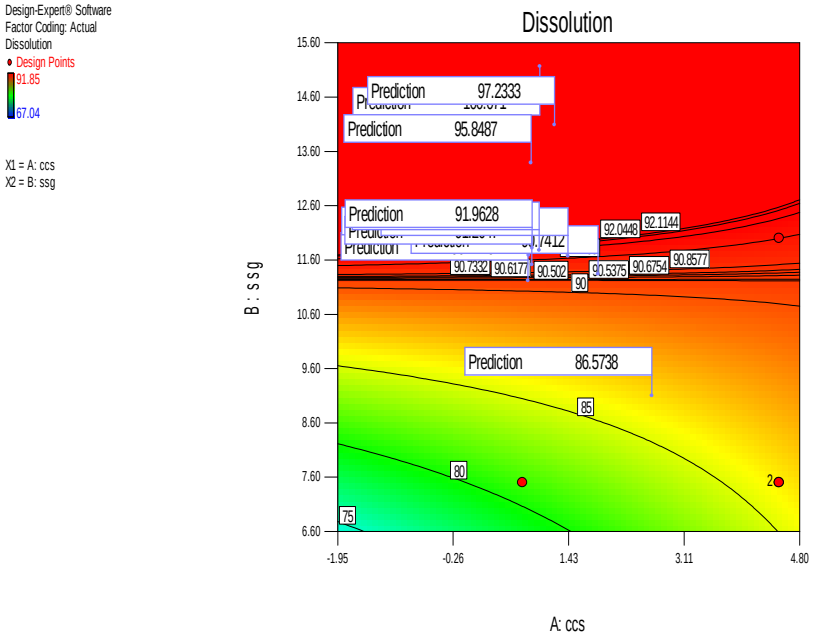
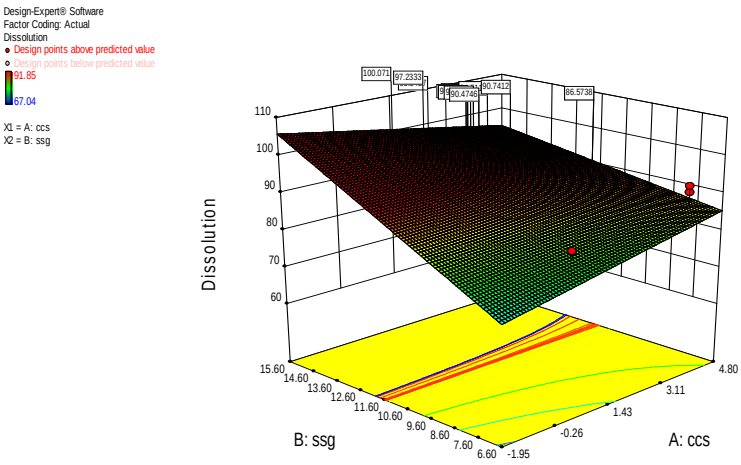


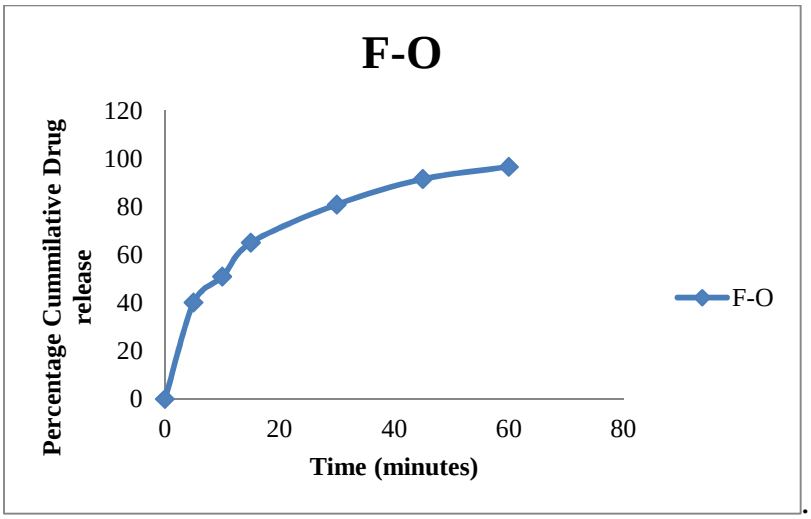

**Figure 13. Dissolution 3D Graph**




## Optimization

Based on the observations using a DESIGN EXPERT 8.0.7.1 a new optimized formula (F-O) was developed using 2.8 mg CCS and 12 mg SSG and evaluate for similar pre compressional, post compressional parameters and compared with F6 formulation. The angle of repose was found to be 25°.96′±0.870 , Hausner's ratio was calculated as 1.2±0.05 and Compressibility index as 16.85±3.91 which indicates good flow property. The post compression parameters weight variation was found to be 249±4.35 which is within limits. Thickness3.16±0.05, Hardness ($Kg/cm^2$)3.66±0.94, Friability(%)0.80, Drug content(%)100.41±0.84, Wetting time(min)0.55, Disintegration time(min)0.48. All the parameters are found to be within range. The disintegration time was achieved within 60min. The *in-vitro* drug release was listed in figure 14. As per the results F-O showed the drug release greater than 80% within 30min and 96.67±1.18 within 60min. F-O showed better drug release compared to other formulations.

**Figure 14. *In-Vitro* drug release for formulation of F-O**




## CONCLUSION

Resposive surface methodology was applied to study the effect of formulation variable on responsive disintegration time and $t_{90\%}$ of drug release in the development of oral disintegrating tablets of Efavirenz by applying computer optimization technique. The percentage and nature of superdisintigrent which is effecting the dintigration time and dissolution. Results demonstrated that high levels of SSG and low levels of CCS has a positive effect on disintegration and dissolution. Among all the two superdisntigrents high level SSG in combination with low level of CCS provided a beneficial results for in the development of oral disintegrating tablets. Further studies required to be carried to obtain the optimal settings.

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