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ORIGINAL RESEARCH

Design of Experiments Assisted Formulation Optimization and Evaluation of Efavirenz Solid Dispersion Adsorbate for Improvement in Dissolution and Flow Properties

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Background: Efavirenz (EFZ) is an anti-HIV drug that has been administered as first-line treatment, which exhibits low solubility and poor oral bioavailability. Therefore, the current study aimed to develop a solid dispersion adsorbate (SDA) to enhance the dissolution rate and flow properties of EFZ for solid oral dosage forms.

Methods: The SDA of EFZ was prepared using the fusion method with PEG-6000 and poloxamer-188 as carriers, along with avicel PH-102 and aerosil-200 as adsorbents. 3^2 full factorial approach was employed to formulate the SDA and evaluate the effects of two independent factors X_1: the ratio of PEG-6000 to EFZ in the solid dispersion, and X_2: the ratio of aerosil-200 to the solid dispersion. The dependent factors analyzed were Y_1: the time required for 85% of the drug release, and Y_2: angle of repose.

Results: The optimized formulation (F9) was selected through numerical optimization, demonstrating the desired drug release and excellent flow properties of the pre-compressed SDA. Fourier transform infrared (FTIR) spectroscopy, Differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Scanning electron microscopy (SEM) of SDA showed the transformation of crystalline to amorphous form of EFZ, which is responsible for improving drug dissolution. The direct compression method was used to prepare SDA-EFZ tablets (equivalent to 25 mg EFZ) along with plain EFZ. The dissolution efficiency increased from 50.68% for plain EFZ tablets to 96.18% for EFZ-SDA tablets. Furthermore, the cumulative percentage drug release (%CDR) from SDA tablets was nearly double that of plain EFZ tablets. Stability testing indicated no significant changes in drug content and %CDR of the SDA tablets.

Conclusion: The findings of this study suggest that the SDA method is an effective approach for enhancing the dissolution and flow characteristics of EFZ and may serve as an alternative strategy for preparing solid dosage forms in commercial applications.

Keywords: solid dispersion adsorbate, efavirenz, factorial design, drug delivery, in vitro dissolution

Introduction

The common problem with the number of active pharmaceutical ingredients (API) is the low and variable dissolution rate and oral bioavailability due to poor aqueous solubility at physiological pH. Efavirenz (EFZ), an antiviral agent, is widely used drugs for the treatment of HIV infection.[1] It comes under the biopharmaceutical classification system (BCS) class II category because of its high permeability and poor water solubility. EFZ is chemically (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1- benzoxazin-2-one 6 (Figure 1).[2] It shows low oral bioavailability (40–45%), which is

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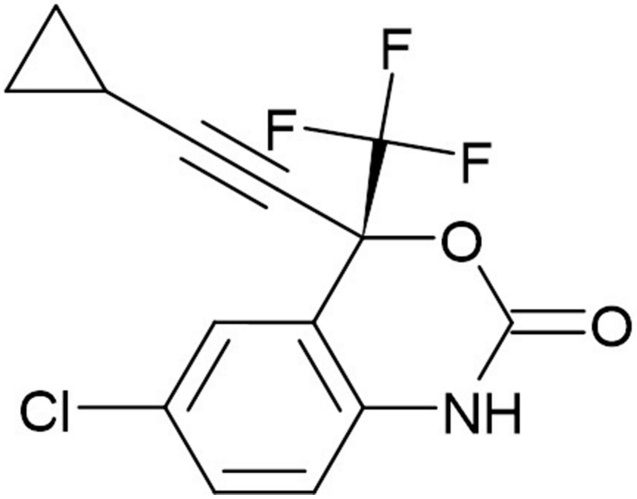

Figure 1 Chemical structure of efavirenz.

practically insoluble over a pH range of 1.2–8.0 and exhibits a pKa of 10.2.[3,4] In such cases, dissolution is the rate-limiting step in drug absorption, and improvement in solubility can augment the bioavailability and reduce variability in the bioavailability of a drug. Several methods have been used to augment the solubility and dissolution rate of EFZ.[5] These include the preparation of microspheres, emulsions, nanosuspensions, self-microemulsions, and solid dispersions (SD). SD denotes the dispersion of one or more water-insoluble drugs in a hydrophilic inert solid base using various methods, including the solvent evaporation method, fusion method, and melting-solvent method.[3,6,7] The formation of SD aids in boosting the bioavailability of drugs by increasing their solubility and dissolution rate in water. The drug molecules remained in a high-energy state in SD. This makes it difficult to compress, pulverize, flow, and return to the crystalline form with reduced solubility during storage.[8] The SD adsorbate (SDA) is a novel hybrid technology that combines melt and SD adsorption to form a free-flowing powder. This method involves the adsorption of SD onto a hydrophilic, high surface area adsorbent, which tends to increase solubility, dissolution rates, and bioavailability.[9,10] The adsorbent also aids in the compressibility of SD, which is used to formulate it as a tablet or capsule dosage form.[11] Nanoscale pores with large surface areas and pore volumes were observed in porous adsorbents. Porous adsorbents/carriers used in pharmaceuticals include porous ceramic, porous silicon dioxide, and magnesium aluminometasilicate (Neusilin).[12,13] The fusion method was used for solid dispersion formulation, because it is simple and economical.[14] This method avoids the use of organic solvents and achieves intermixing of drugs with polymer at the molecular level. Thus, the absence of the risk associated with the residual solvents is one of the advantages of this method. Easy processing is an added benefit because no special treatment is needed to bring the melt mixture to a solid state.[15]

The Design of Experiment (DoE) is an effective statistical method for variable selection and optimization.[16] It is based on the simultaneous adjustment of several elements to determine the parameter configuration that maximizes one or more outputs of interest while requiring the fewest experimental runs for testing, resulting in overcoming the time, effort, and financial barriers that have traditionally been major hurdles in formulation research.[17,18] Plackett-Burman, Fractional Factorial Design, Full Factorial Design (FFD), and Response Surface Methodology are some of the most common DoE approaches used in pharmaceutical product development. FFD is the best method for investigating several intervention components because it improves model prediction ability by estimating the major effects from the average of other effects.[19,20]

The current study aimed to formulate and optimize the SD of EFZ to enhance the dissolution of the drug with the fusion method using PEG-4000, PEG-6000, and Poloxamer-188 as solubilizers for the SD formulation. A three-level, two-factor (3^2) FFD was used to optimize the formulation and identify the main effect and interaction effect between the examined components on dissolution and flow properties. The secondary goal was to adsorb the melt dispersion onto a porous adsorbent to transform it into free-flowing and compressible granules. Adsorption on porous adsorbent also enhances the surface area, which contributes to improving the dissolution rates. Avicel PH-102 and aerosil-200 were used as adsorbents, as both adsorbents are reported to have good adsorptive properties.[21] The optimal formulation was chosen

by numerical optimization and evaluated using Fourier transform infrared (FTIR) spectroscopy, Differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM), and in vitro dissolution analysis. The optimized SDA was formulated as a tablet and characterized, including the stability testing of the optimized formulation.

Materials and Methods

Materials

Efavirenz (Glenmark Pharmaceuticals Ltd., Mumbai, India), Aerosil-200 (Mylan Labs, Hyderabad, India), and Spray dried lactose (Cipla, Mumbai, India) were obtained as gift samples. PEG-4000, PEG-6000, Poloxamer-188, Avicel PH102 (microcrystalline cellulose), talc, and magnesium stearate were purchased from S.D. Fine Chemicals Ltd. India. All other compounds used in this study were of analytical grade.

Solubility Study of Efavirenz

The saturation solubility of the drug was examined in 0.1 N HCl, acetate buffer (pH 4.4, 6.4, 6.8, and 7.4), and distilled water. The maximum amount of drug was added to 10 mL of the above media separately in 25 mL amber-colored volumetric flask and kept at an orbital shaker bath. Shaking was performed for 24 h at 50 rpm and 37 ± 0.5°C.[22] The samples were collected and passed through a 0.22 µm syringe filter. The filtrate was suitably diluted with the same solvent, and then the absorbance of EFZ was measured at 247nm using a validated UV-spectrophotometric procedure.[23] The linearity was obtained in the range of 3-15 µg/mL and showed a good linear relationship with $R^2 = 0.9827$.

Screening of Carriers Based on Phase Solubility Studies

The solubility of EFZ in PEG-4000, PEG-6000, and Poloxamer-188 was evaluated as previously described methods.[24] In separate volumetric flasks, 10 mL of 4%, 6%, 8%, 10%, and 12% solutions of each polymer in water was taken. EFZ was added in excess quantity to each of the above-mentioned solutions and was kept on a shaker for 24 hrs at 37 °C. The solutions were then filtered using Whatman's filter paper. UV-spectrophotometric (Shimadzu U-1800, Japan) was used to quantify the amount of dissolved drug in the sample. Stability constants were calculated using Higuchi-Connors theory.[25]

The apparent stability constant was computed using the following formula.

$$K_s = \frac{Slope}{S_o\,(1 - Slope)}$$

Gibbs' free energy of transfer (ΔG°) values (distilled water to polymer solution) were calculated using the following formula:

$$\Delta G^{\circ} = -2.303RT\,\log\frac{S_o}{S_s}$$

S_o – Solubility of EFZ in polymer
S_s – Solubility of EFZ in water

Formulation of Solid Dispersion (SD)

Screening of Carrier to EFZ Ratio in SD

We used PEG-6000 and Poloxamer-188 as carriers/hydrophilic solubilizers to prepare SD. These are commonly used carriers in preparing SD as they possess good surfactant properties, low melting point (~58–63°C), and adequate safety for oral consumption.[26,27] These are FDA-approved excipients used to lower viscosity, improve wettability, and increase stability.[28] Pilot batches of EFZ SD were prepared using the fusion method, and different carriers to EFZ ratios of 0.25:1, 0.50:1, 0.75:1, 1:1, and 2:1 were tested in SD formulation. These different ratios were tested for each carrier, resulting in 10 trial batches. The carrier was melted in a petri dish, and the EFZ was dispersed by continuous stirring on the melted carriers. The content in the petri dish was instantly cooled to room temperature to obtain SD, which was then collected, sifted, and stored in a desiccator until subsequent analysis.

Screening of Adsorbent to SD Ratio

Avicel PH-102 and Aerosil-200 were used as adsorbents to improve the flow characteristics of the SD. Aerosil-200 has an adsorption capacity of 3.2 mL/g and a surface area of 300 m^2/g. It is used as a free-flowing agent to enhance the properties of the powders. It also improves the distribution of active pharmaceutical ingredients.[29] The selected EFZ-SD formulation was adsorbed onto avicel PH-102 and aerosil-200 separately at different ratios to prepare EFZ-SD adsorbate (SDA) granules. The angle of repose of EFZ-SDA granules was measured using the fixed funnel method.

Preparation of EFZ-SDA Granules

EFZ-SD was prepared as described in the previous section using PEG 6000 as a carrier, which was chosen based on an earlier investigation. The PEG 6000 was melted in a porcelain dish on a water bath at 60°C. EFZ was added to the molten carrier and dispersed by stirring. During the dispersal of EFZ in PEG 6000, the mass shall be maintained at 60°C to achieve uniform distribution of EFZ in a carrier.[22] Adsorbent (aerosil-200) was then added to the molten mixture and mixed. This mass was allowed to cool and dry at room temperature to produce SDA. The dried SDA was passed through a sieve. 20 to obtain SDA granules.[30] SDA granules were stored in a desiccator until subsequent analysis.

Experimental Design

To measure the influence of the two independent factors on dissolution and flow properties, we used a three-level, two-factor (3^2) FFD with the Design-Expert program version 13 (Stat-Ease, Inc., Minneapolis, MN). The numbers −1, 0, and +1 were used to designate the low, medium, and high degrees of each variable, respectively. The independent variables chosen were the ratio between the carrier (PEG-6000) and EFZ in the SD, denoted by X_1, and the ratio between the adsorbent (Aerosil-200) and SD, denoted with X_2. FFD suggested nine formulations as shown in Table 1. Dissolution characteristics (time needed for 85% drug release - t_{85}: Y_1) and flow characteristics (angle of repose: Y_2) were chosen as dependent variables. The responses were calculated using an interactive and polynomial statistical model as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}{X_1}^2 + b_{22}{X_2}^2$$

In the above equation, the dependent variable is denoted by Y, and the average response across all trials is denoted by b_0. The predicted coefficients for the factors X_1, X_2, and X_1X_2 are denoted as b_1, b_2, b_{11}, b_{12}, and b_{22}. They depicted the mean result of varying each factor from the lowest to the highest value individually. X_1X_2 is an interaction term that

Table 1 3^2 FFD Layout of Different Batches of SDA Formulation

Formulation Code	Independent Variables	
	X_1[a]	X_2[b]
F1	1:0.75	0
F2	1: 0.75	1
F3	1:0.75	2
F4	1:1	0
F5	1:1	1
F6	1:1	2
F7	1:2	0
F8	1:2	1
F9	1:2	2

Notes: X_1[a]: SD was formulated using the ratio of drug to carrier; X_2[b]: A portion of these SD was adsorbed into varied ratios of aerosol.

demonstrates how responses change when two factors are altered simultaneously. To explore the non-linearity in a relationship, polynomial terms (X_1^2, X_2^2) were added.[31] The Design-Expert software enabled the production of polynomial equations and all significant values. The control of variables influencing the outcomes was also evaluated. Polynomial equations for the influenced variables, *viz.*, drug release and the angle of repose, were determined. Non-significant coefficients were eliminated to simplify the generated polynomial equations. To confirm the experimental data, we used analysis of variance (ANOVA) and the F-test. Graphical optimization and the overlay plots were used to select the ideal preparation.[32]

Characterization of SDA

Fourier Transform Infrared (FTIR) Analysis

Potassium bromide (KBr) press was used to compress the powder at 20 psi for 10 min to form the pellets of pure EFZ, PEG-6000, PEG-6000 SD, Aerosil 200, and SDA. The samples were scanned using an FTIR spectrophotometer (Alpha, Bruker, Germany) over the scan range of 4000 cm^{-1} to 400 cm^{-1}.[33,34]

Differential Scanning Calorimetry (DSC) Analysis

The thermal behavior of the EFZ, PEG 6000, and SDA was investigated using a DSC instrument (DSC60 Shimadzu, Japan). The samples were weighed and sealed in a sample pan and then heated at a rate of 10° C/min in an inert environment flushed with dry nitrogen. Thermal behavior was investigated for a temperature range of 35–300 °C.[34,35]

X-Ray Diffraction (XRD) Analysis

PEG-6000, EFZ, and SDA were grounded into powder in a mortar and pestle. The XRD spectra of the powdered samples were recorded in a Philips X-ray diffractometer with scanning angle spanning between 0° and 40° of 2θ.[20,35]

Surface Morphology Analysis

The morphological features of EFZ and SDA were evaluated using scanning electron microscopy (SEM) (Model - XL30 ESEM with EDAX, Philips, Eindhoven, Netherlands). Using 10 mA current, the dried EFZ and SDA were gold-coated using a sputter cutter. After gold coating, the sample was viewed at different magnifications at a voltage of 15 kV.[36,37]

Determination of Drug Content Uniformity in SD and SDA

SD and SDA equivalent to 10 mg of EFZ were solubilized in 50 mL of methanol. Then, 1 mL solution was withdrawn and diluted 10 times with methanol. The absorbance of the sample was measured at 247 nm using UV-visible spectrophotometry to determine the amount of drug content.[38]

In vitro Dissolution Studies of SD and SDA

The in vitro dissolution tests were carried out for the SD and SDA with a USP Type 2 (paddle) dissolution apparatus with 900 mL of 1% w/v sodium lauryl sulfate (SLS) solution.[39] SLS was used in a dissolving medium because of its ability to maintain sink conditions with poorly water-soluble drugs.[40] The SD and SDA equivalent to 25 mg of EFZ were placed in dissolution media. The temperature was maintained at 37±0.5°C, and the paddle speed was 50 rpm. 5 mL of the solution was removed at each interval, and each aliquot was replaced with an equal volume of fresh dissolving medium. The aliquots were filtered and spectrophotometrically measured at 247 nm. The dissolution tests were carried out in triplicate. The percent drug release was calculated by comparing the absorbance of the diluted aliquots, and the dissolution profile was obtained by plotting the percent drug release against time.

Preparation of Tablets

The EFZ-SDA tablets were prepared using the direct compression method. Table 2 shows the compositions of SDA and plain EFZ tablets. The optimized formulation of SDA granules was blended thoroughly for 10 min with sodium starch glycolate and microcrystalline cellulose. The mixture was blended with magnesium stearate and talc for another five minutes and compressed using a rotary tablet machine. The prepared tablets were examined for different quality control tests, such as hardness, friability, and weight variation.[41]

Table 2 Formula of SDA Tablets and Plain EFZ Tablets

Ingredients	SDA Tablets (mg)	Plain EFZ Tablets (mg)
Efavirenz	287*	25
Microcrystalline cellulose	184	447
Sodium starch glycolate	19	18
Magnesium stearate	5	5
Talc	5	5
Total weight	500	500

Note: *Optimized batch of SDA granules (F9) equivalent to 25 mg EFZ.

Stability Studies

The stability of the formulation was determined according to ICH guidelines Q1A (R2).[42] The optimized formulation was kept in a stability chamber for six months at 40±2°C and 75±5% RH for accelerated stability studies. The samples were placed in vials that were sealed using rubber plugs and aluminum caps. After the stability period, the samples were removed, and in-vitro parameters were evaluated.[43]

Results and Discussion

Phase Solubility Analysis

The solubility of EFZ in 0.1 N HCl, acetate buffer (pH 4.4, 6.4, 6.8, and 7.4), and distilled water was assessed. EFZ is sparingly soluble in water and slightly soluble in HCl or acetate buffer (Figure 2A).[44] The drug did not show pH-dependent solubility in GI tract pH conditions. EFZ is hydrophobic and contains functional groups such as Cl, CF3, cyclopropane, and alkyl groups as shown in Figure 1. It has an NH, which can be protonated, but NH-C=O makes it enol enol-extended conjugation. With a pKa of 10.2, the drug is weakly basic, and a log P value of 4.6 indicates the low solubility of EFZ. A phase solubility analysis was conducted to determine the solubility of EFZ in three polymeric carriers (PEG-4000, PEG-6000, and poloxamer-188) to select the best carrier for the formulation of SD (Figure 2B). For each polymer, it was observed that an increase in their concentration from 4% to 12% resulted in an increase in the solubility of EFZ, but EFZ demonstrated noticeably greater solubility in poloxamer-188 and PEG-6000 compared to PEG-4000. The regression coefficient (R^2) for EFZ in PEG-4000, PEG-6000, and poloxamer-188 were 0.9726, 0.9812, and 0.9826, respectively, indicating a good correlation between the variables.

Gibbs' free energy (ΔG°) is associated with the energy that determines whether a reaction will be spontaneous or not. Negative Gibbs free energy transfer values show the spontaneous solubilization process. While ΔG° values were calculated from the solubility of EFZ in pure distilled water and the polymer solution, the stability constant was estimated using the phase solubility graph. Table 3 shows the spontaneous solubilization of EFZ in the polymer solution as indicated by the negative ΔG° value. More negative ΔG° values were recorded for poloxamer-188 and PEG-6000 than for PEG-4000. Poloxamer-188 exhibited a higher stability constant than those of PEG-4000 and PEG-6000. The stability constant was affected by the slope values. The solubilization of the drug by the polymer is directly proportional to its slope.[45] Based on these results, we selected PEG-6000 and poloxamer-188 as the carrier for SD preparation.

Effect of Concentration of Carriers on Drug Release

The in vitro dissolution pattern of EFZ with Poloxamer-188 or PEG-6000 SD at various ratios and per se EFZ is shown in Figure 3. As the proportion of carriers to the drug increased from 0.25:1 to 2:1, an increase in the cumulative drug release was observed. Drug release from formulations with carrier-to-drug ratios of 0.75:1, 1:1, and 2:1 did not differ significantly. However, an analysis of the dissolution profiles indicated that an increase in the proportion of carriers increased the amount of drug released during the given period.[45] The release of EFZ from SD with PEG-6000 as the

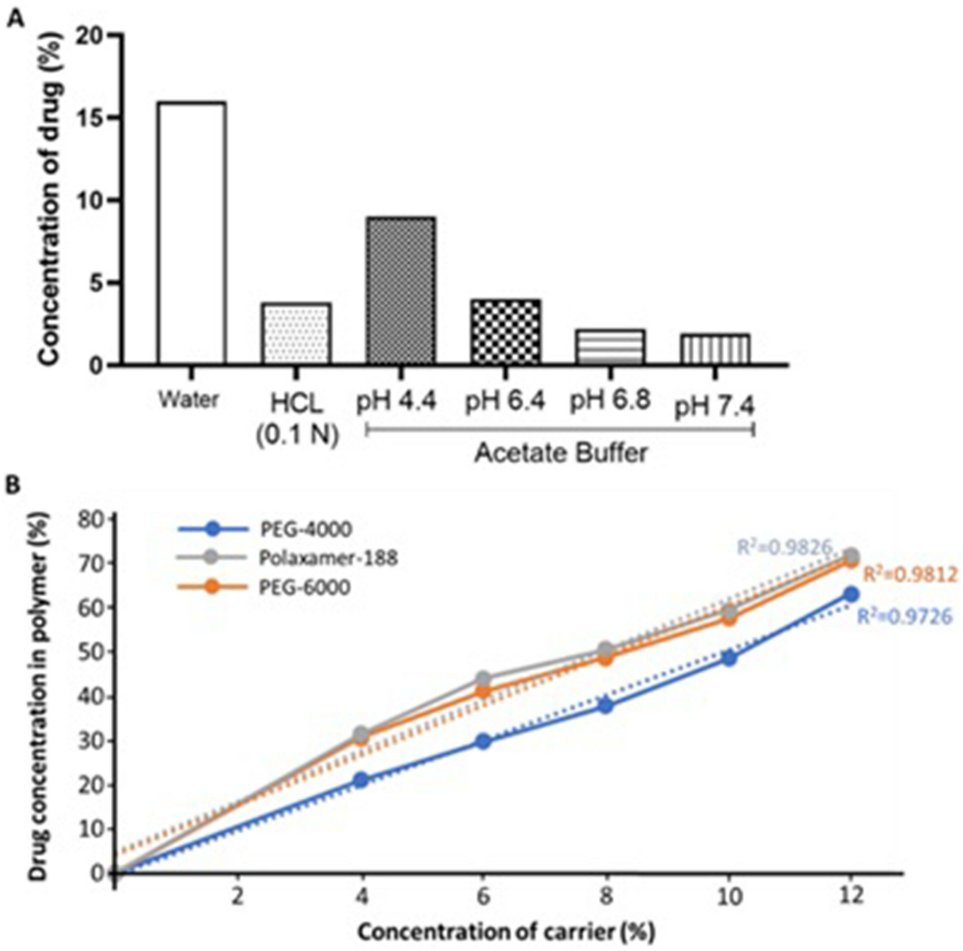

Figure 2 (**A**) Solubility of efavirenz in different solutions and (**B**) Phase solubility studies of EFZ in three different polymers, PEG-4000, Poloxamer-188, and PEG-6000, of varying concentrations. Solid lines show the actual concentration of the drug in the polymer solution.

carrier was higher than that from SD with poloxamer-188. Thus, SD with a 2:1 ratio of PEG-6000 to the drug was selected for the optimization process in the preparation of SDA.

Selection of Adsorbent to SD Ratio

The prepared SD exhibited poor flow properties and compressibility, which made it challenging to pulverize. To improve the flow properties of SD, we used aerosil-200 and avicel PH-102 as adsorbents, owing to their good adsorptive properties. When

Table 3 Gibbs Free Energy for EFV in Different Carrier Solutions

Carrier concentration (%)	ΔG° (KJ/mol) at 37°C		
	Poloxamer 188	PEG 6000	PEG4000
4	−1.045	−0.983	−0.809
6	−1.106	−1.016	−0.843
8	−1.249	−1.095	−0.881
10	−1.265	−2.44	−1.05
12	−1.455	−2.87	−1.105
K_s	0.530	0.515	0.442

Note: K_s: Stability constant.

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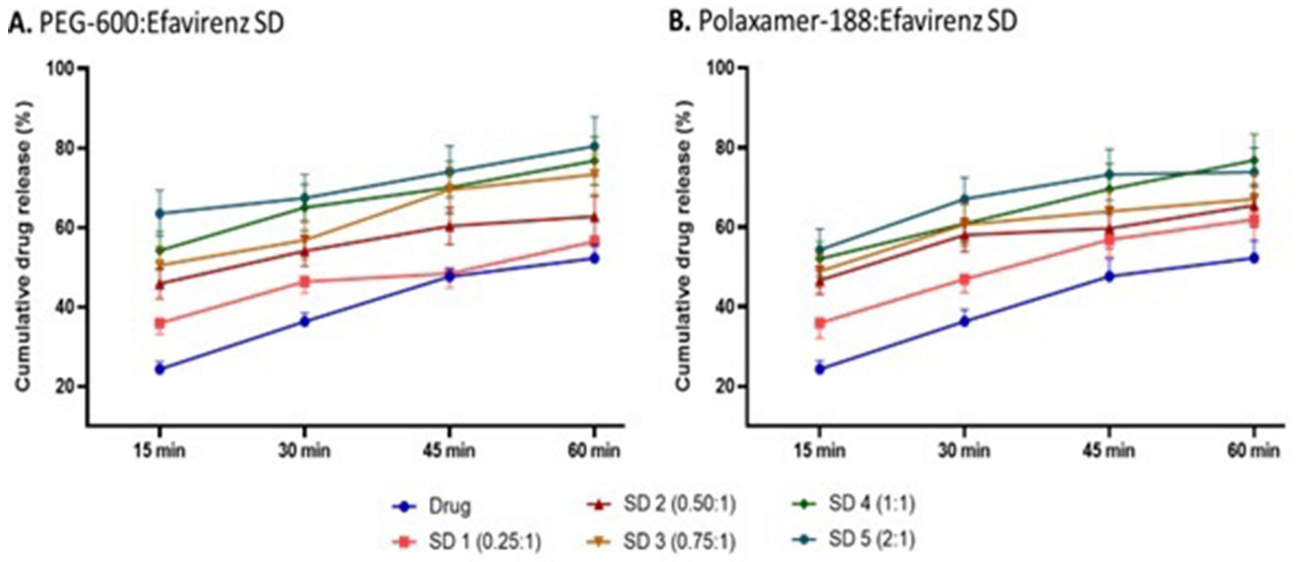

Figure 3 Effect of different ratios of PEG-6000 (**A**) and Poloxamer-188 (**B**) on the release of efavirenz from its SD formulation. Each formulation is prepared by using the varying carrier-to-drug ratio (0.25:1, 0.50:1, 0.75:1, 1:1, and 2:1). Amount of drug release from the SD filled in capsules is quantified at 15, 30, 45, and 60 min interval from each batch of SD and cumulative drug release (%) was plotted against the time.

SD was adsorbed onto Aerosil-200, the angle of repose values decreased significantly compared with the results obtained from SD adsorption on avicel PH-102 (Figure 4). The angle of repose of the SDA prepared with aerosil-200 was less than 25°, indicating good flow properties. This result was not observed when avicel PH-102 was used as an adsorbent for EFZ SD, with an angle of repose in the range of 27° to 34°. This may be ascribed to the greater specific surface area of aerosil-200 (200 ± 20 m^2/g) than that of Avicel PH102 (1.21–1.30 m^2/g).[46] This allowed for a larger adsorption on the surface of Aerosil-200. A significant improvement in the flow property and reduction in the angle of repose were observed when the ratio of adsorbent to SD was increased from 2:(2:1) to 3:(2:1). However, no such improvement in flow was observed with a further increase in the adsorbent to SD ratio from 3:(2:1) to 4:(2:1). A further increase in the ratio was not observed as the results were approached constancy. Furthermore, given the bulky nature of aerosil-200, higher proportions of aerosil-200 were not considered to minimize the bulk volume of the formulation.

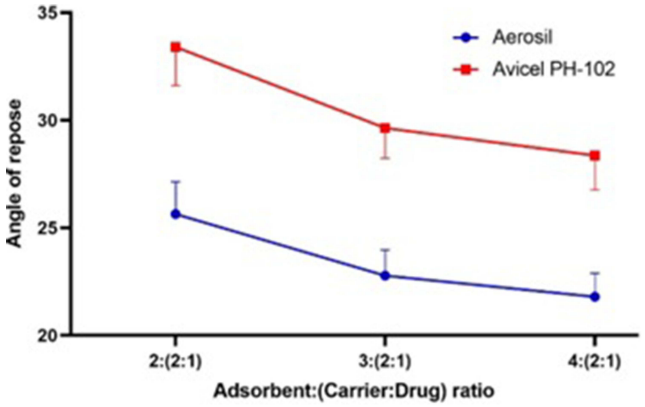

Figure 4 Influence of different adsorbents on angle of repose. Carrier to drug ratio was kept constant at 2:1, adsorbent concentration was increased from 2 to 4, and angle of repose was measured.

Evaluation of the Effect of Formulation Variables on t85 (Y_1) Using Factorial Design

Figure 5 depicts the response surface plot, which reveals the correlation between independent variables and the time required for drug release to reach 85% (t_{85}). For nine developed formulations (F1-F9), t_{85} was in the range of 81.58 to 90.35 min. The cumulative drug release (%) of all nine formulations was estimated, and we observed that all formulations showed a good release pattern, releasing more than 85% drug in 30 min, except formulations F1, F3, and F5 (Table 4). Table 5 describes the built-in equation that connects the response t_{85} (Y_1) with the transitioned factor. The model was significant, as indicated by the ANOVA results. For response t_{85}, the correlation coefficient (r^2) is 0.9832, indicating a good fit. The generated polynomial equations were simplified ($p>0.10$) by removing insignificant coefficients. The coefficients with p values less than 0.05 were kept. Consequently, the following polynomial equation was derived as part of a reduced model for t_{85}.

$$t_{85}(Y_1) = +86.65 - 3.601\,X_1 + 4.38\,X_2 + 3.732\,X_1\,X_2 + 7.527\,X_1^2$$

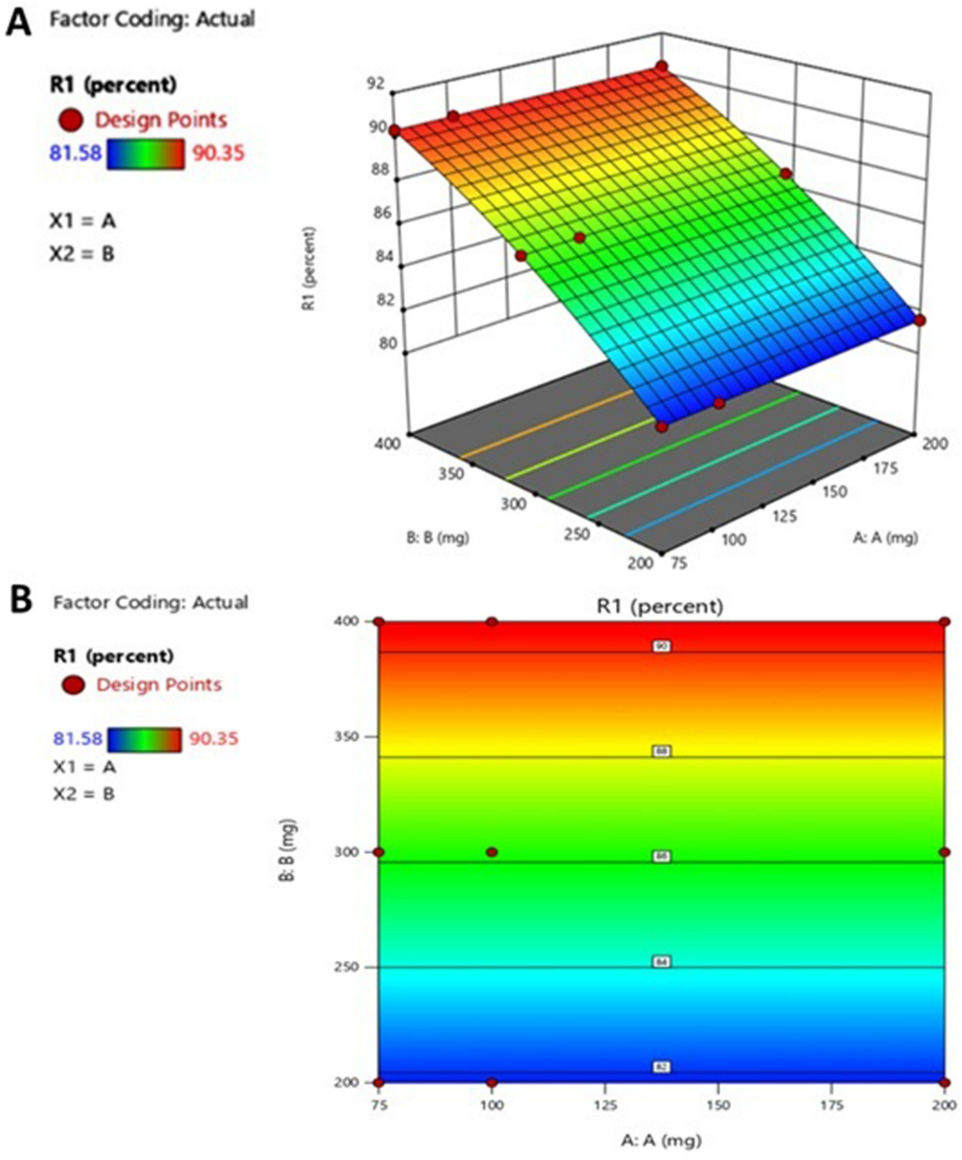

Figure 5 (**A**) Response surface plot and (**B**) Contour plot for the influence of different adsorbents on drug release of SDA.

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Table 4 Percent Drug Release and Angle of Repose of SDA Formulations

Formulations	Drug Release (%)	Angle of Response (°)
F1	81.58	25.64
F2	90.35	21.8
F3	81.58	25.64
F4	86.65	22.78
F5	81.58	25.64
F6	86.65	22.78
F7	90.35	21.8
F8	86.65	22.78
F9	93.36	21.8
% bias	3.56	2.85

Table 5 Polynomial Equation Derived for Dependent Responses

Observed Response	b_0	X_1	X_2	X_1X_2	X_1^2	X_2^2	R^2	F
% Drug Release (Y_1)	86.65	−3.60	4.38	3.73	7.53	−0.685	0.983	368.82
p-value	0.004	–	–	–	–	–	–	–
Angle of repose (°) (Y_2)	22.78	−1.48	−1.92	1.52	3.82	0.94	0.846	37.55
p-value	0.004	–	–	–	–	–	–	–

In the condensed model, the value of the coefficient X_1 has a negative sign. The condensed model showed that the ratio between carrier and drug (X_1) was inversely proportional to the t_{85} value. The t_{85} values for all formulations were found to be less than 30 min except for trials F1, F3, and F5. The decrease in t_{85} may be associated with the wetting effect of the carrier and micellar solubilization.[47]

Evaluation of the Influence of Formulation Variables on Flow Characteristic (Y_2) Using Factorial Design

The association between the independent factors and the angle of repose varied from 21.80 to 25.64 for all nine formulations (F1-F9) (Table 4), according to the response surface plot (Figure 6). Table 5 presents the fitted equation that explains the relationship between the response (Y_2) and the transformed factor. A high coefficient and F value indicate that the regression model fits the data well. The correlation coefficient (r^2) for the angle of repose was >0.9, indicating the goodness of fit of the model. Nonsignificant terms (p>1.0) were removed from the polynomial equation to run the model. We kept the coefficients with p values < 0.05. Consequently, the following polynomial equation was derived from a reduced model for the angle of repose.

$$\text{Angle of repose}\,(Y_2) = +22.78 - 1.48\,X_1 - 1.92\,X_2 + 1.529\,X_1X_2 + 0.94\,X_2^2$$

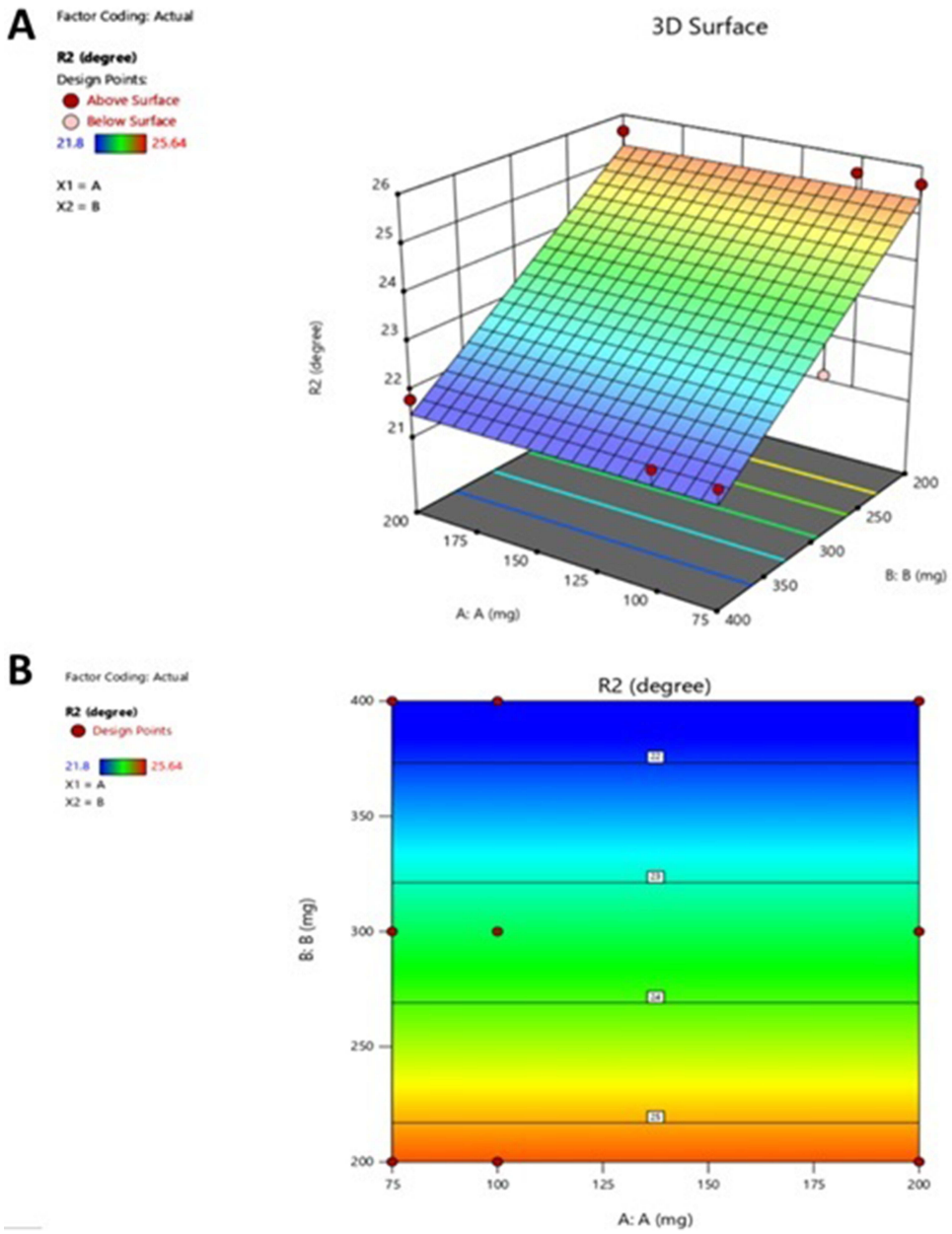

Figure 6 (**A**) Response surface plot and (**B**) Counter plot for the angle of repose of SDA.

A negative value for the coefficient X_2 (−1.92) indicates that it significantly affects the angle of repose. In addition to formulations F1, F3, and F5, the angle of repose given in Table 4 was less than 25° for all formulations. Trials F1, F3, and F5 had poor flow properties and compressibility compared with the remaining trials because they were not adsorbed onto the aerosil-200, making them difficult to pulverize. According to reports, aerosil-200 is a porous calcium silicate with many surface-located interparticle (12 µm) and intraparticle (0.15 µm) pores. This increased the surface area available for the adsorption of SD and enhanced the flow characteristics.[48] The simplified model demonstrated a decrease in the angle of repose with an increase in the ratio of the adsorbent to SD (X_2). An angle of repose below 25° indicated excellent flow characteristics. These findings support the previously published literature.[49]

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Checkpoint Batch

To confirm the precision of the model and the contribution of the generated polynomial equation to response prediction, a checkpoint set was established. Theoretical values were determined by varying the values in the polynomial equation. Following that, the experimental and predicted results were compared at a 95% confidence level and reported as a percentage of bias (Table 4). There was no discernible difference between them; hence, the model was verified because the percentage bias value was below 4%.

Selection of Optimization Batch

All responses with various targets were optimized using graphical optimization (overlay plot, Figure 7). Constraints on the results of the dependent and independent variables led to the creation of an ideal formulation. The constraints of the % cumulative drug release minimum (80% at 60 min) and angle of repose maximum (25°C) were common for all formulations. Design-Expert software was used to calculate the suggested levels of independent variables. The design

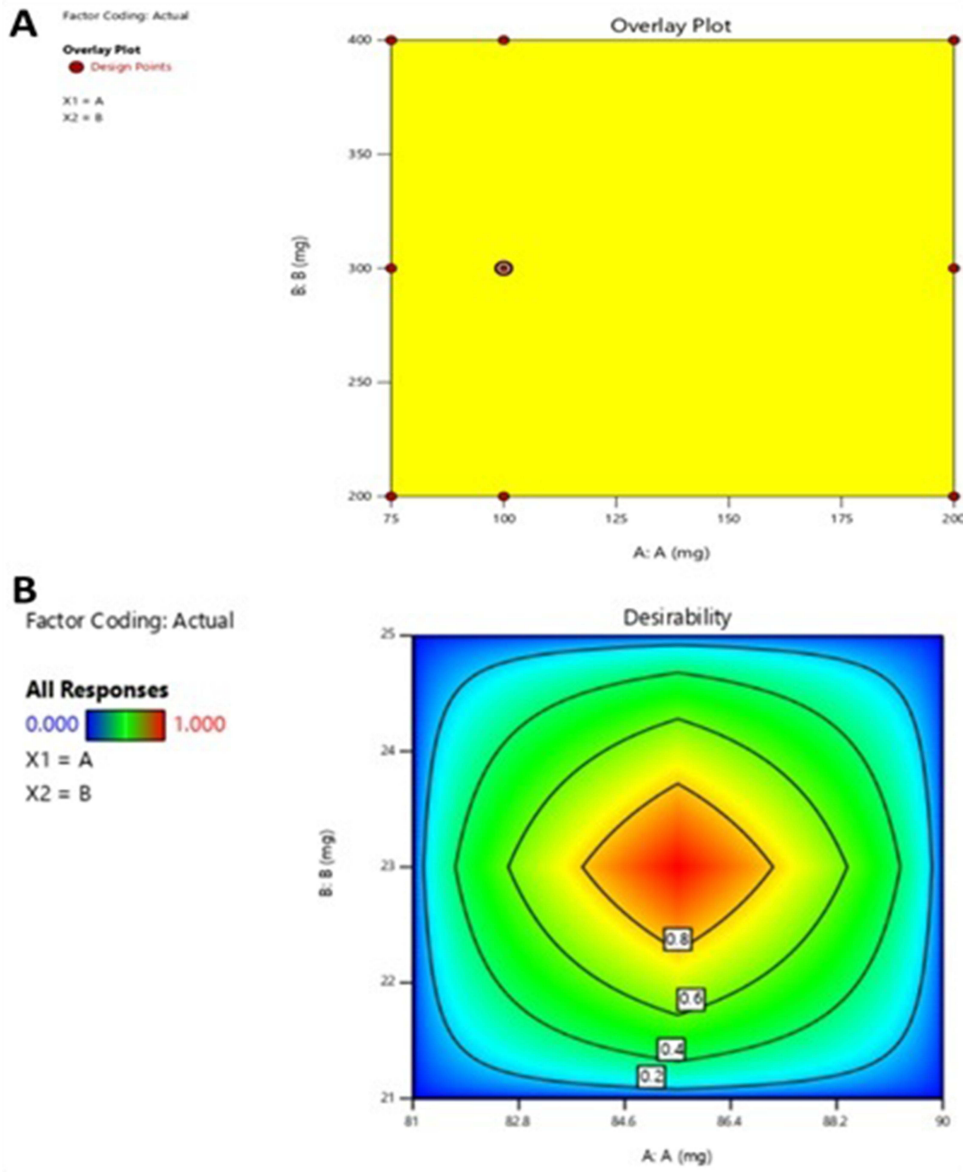

Figure 7 Optimization of SDA granules using (**A**) an overlay plot and (**B**) a desirability plot.

space is visible in the white area of the overlay plot. The optimized batch for the applied constraints was at the upper spot of the design space. As an optimized formulation, F9 is recommended to maintain both independent values at an optimum value.

Characteristics of Optimized Formulation

FTIR Spectroscopy Analysis

FTIR spectroscopy was used to examine the possible interactions between the drug and the chosen polymer.[50] FTIR peaks for the pure drug, PEG-6000, SD, and SDA revealed that there had been no alterations in the positions of the characteristic absorption peaks, which signifies no changes in the bonds of the various functional groups present in the drug (Figure 8). The FTIR spectra of EFZ showed the characteristic bands at 3318.5 cm-1 (for N–H) and 1749.47 (for C=O).[51] The FTIR spectra of the SDA formulation contained all the peaks related to the functional groups of the drug and PEG-6000. The drug and PEG bond were formed, according to the FTIR peak near 1600 cm^{-1} in the case of FTIR spectra of PEG 6000 SD formulation.[52] A peak near 1600 cm^{-1} on the FTIR spectrum of PEG 6000 SD denotes the PEGylation.[53] There were slight variations in the drug's peak intensities in FTIR spectra of SDA formulation at 3318 cm^{-1} and 1749 cm^{-1} (the distinct peak of EFZ). This implied that intermolecular hydrogen bonding or Van der Waals interactions between the drug and polymer might enhance the solubility of a drug.[54] The formed hydrogen bond between the drug and polymer can easily break down in biological fluids, which results in higher drug release and solubility of the developed formulation.

DSC Analysis

The DSC thermograms of EFZ, PEG 6000, and SDA granules (F9) are presented in Figure 9. The EFZ showed a sharp endothermic peak at ~139°C (Figure 9A). This peak corresponded to its melting point and demonstrated its crystallinity. A similar DSC profile for EFZ was reported previously with the same melting point.[55] Similar to a previous study, PEG 6000 exhibited a sharp endothermic peak at 63°C, which corresponded to its melting point (Figure 9B).[56] The thermogram of SDA granules (F9 formulation) did not show any melting endotherm because of the conversion of

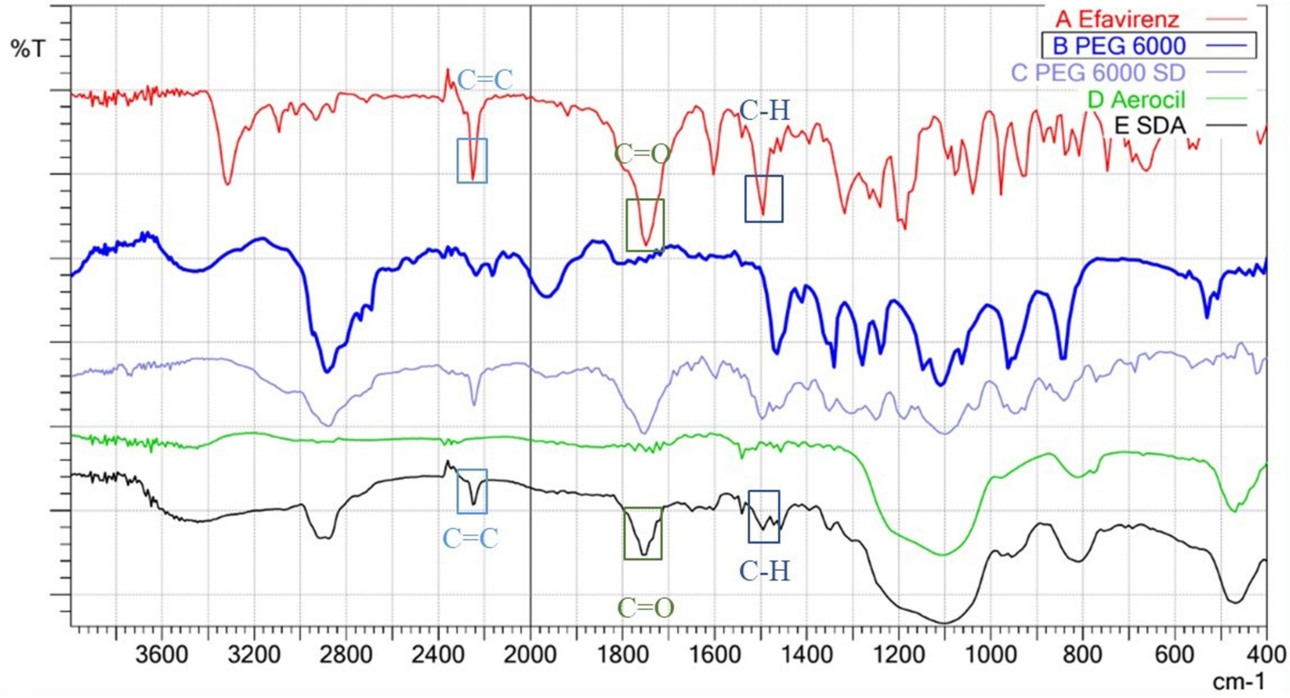

Figure 8 Fourier transform infrared spectra of (**A**) pure efavirenz, (**B**) PEG-6000, (**C**) PEG-6000 SD, (**D**) Aerosil 200, and (**E**) SDA confirm the intermolecular hydrogen bonding or Van der Waals interactions between the drug and polymer.

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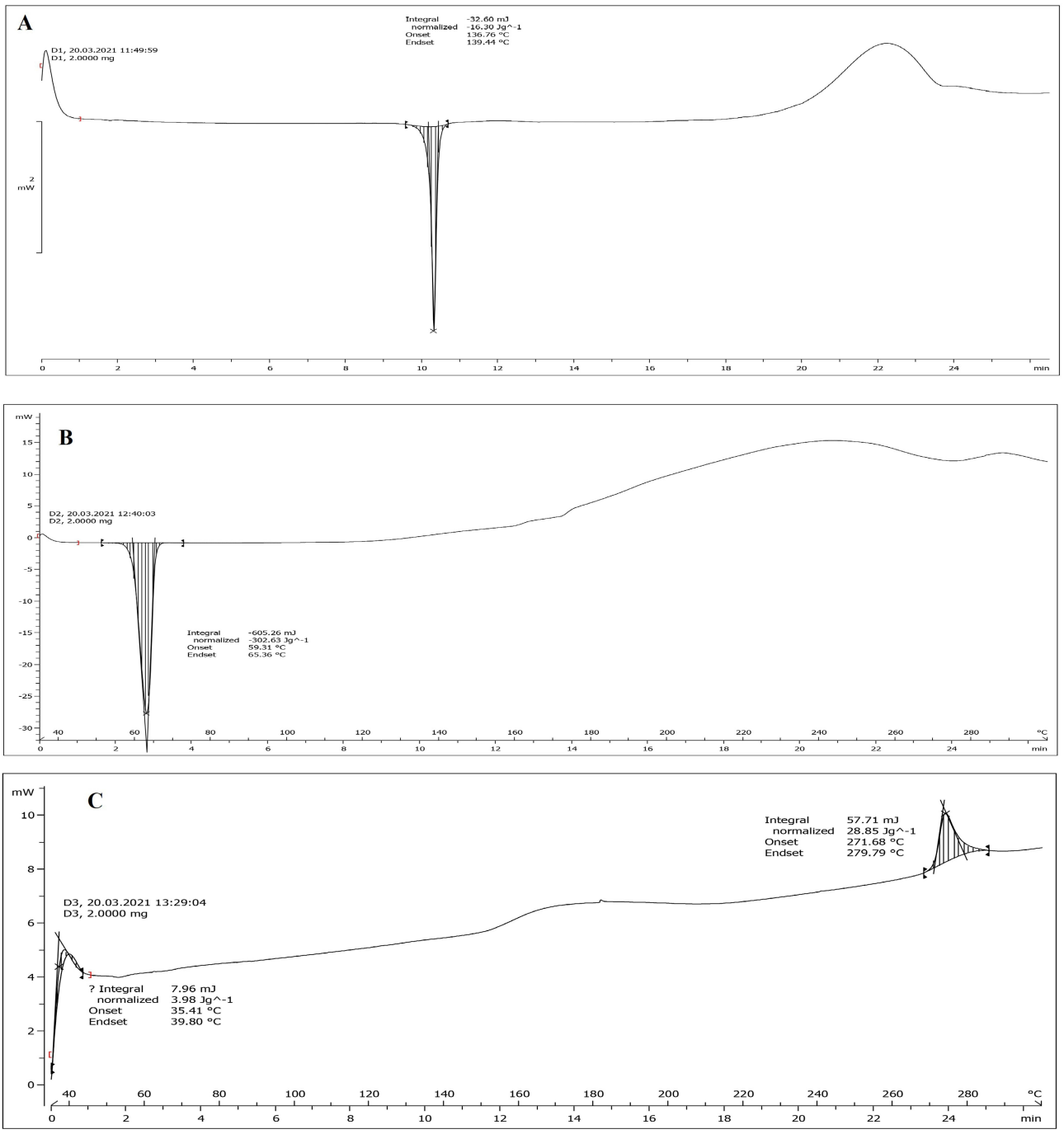

Figure 9 Differential scanning calorimetry thermogram of (**A**) EFZ, (**B**) PEG-6000, and (**C**) SDA granules (F9 formulation) show no thermal peak of EFZ, indicating conversion of EFZ into an amorphous form.

EFZ into an amorphous form (Figure 9C). These results indicate that the crystalline nature of the drug was reduced with the fusion method to form SD using PEG-6000 as carriers.

XRD Analysis

The XRD pattern of the EFZ revealed several distinct peaks at angles of 6.053, 10.37, 10.92, 12.21, 13.10, and 14.10 (Figure 10A), signifying its crystalline nature.[57] The XRD pattern of PEG-6000 revealed a distinctive collection of diffraction peaks. These peaks were observed at angles of 13.45, 14.43, 14.84, 17.01, and 18.87 (Figure 10B). The

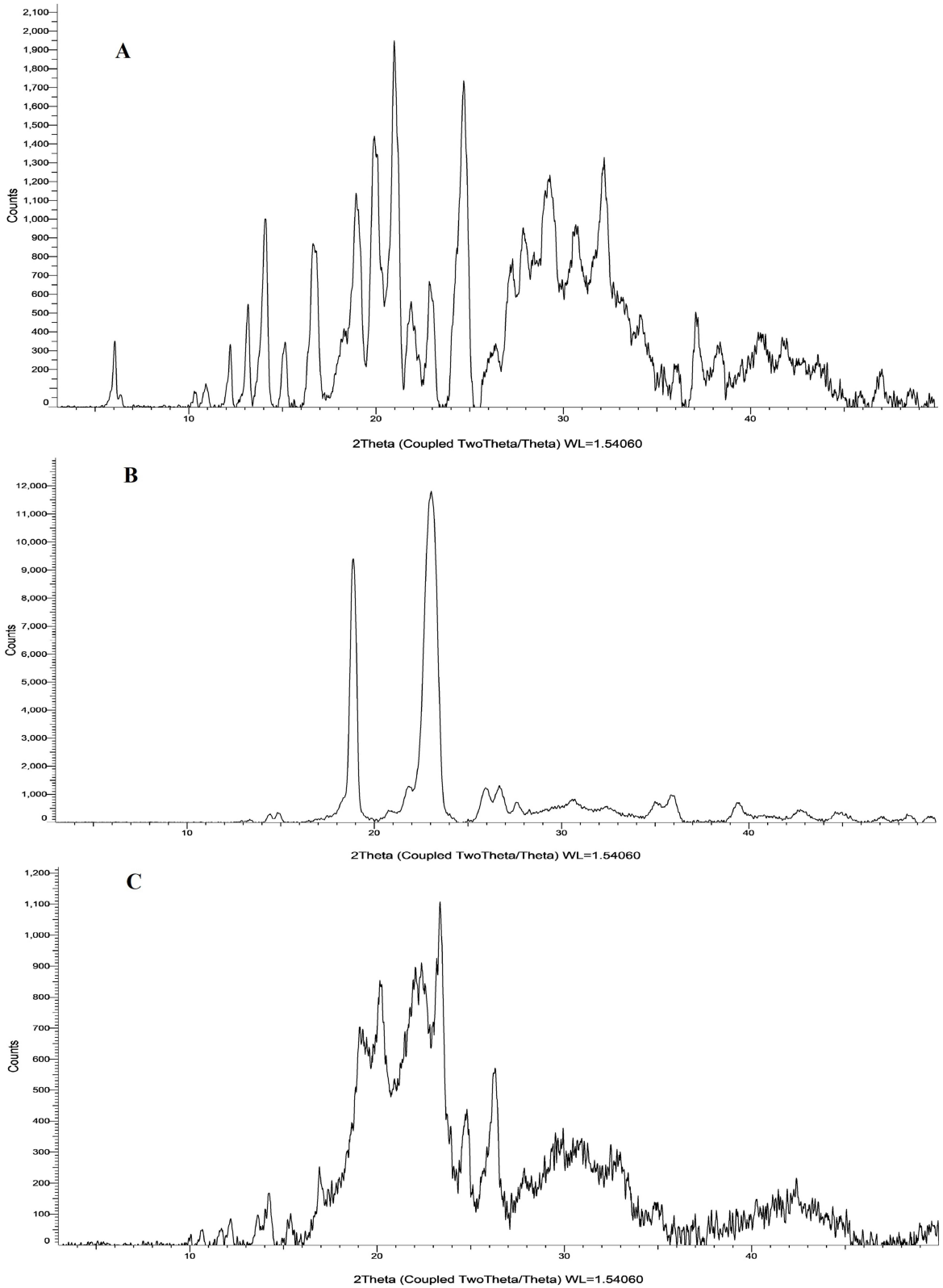

Figure 10 X-ray diffraction pattern of (**A**) EFZ, (**B**) PEG-6000, and (**C**) SDA granules (F9 formulation). SDA formulation shows the absence of distinctive peaks of EFZ, which infers a decrease in drug crystallinity.

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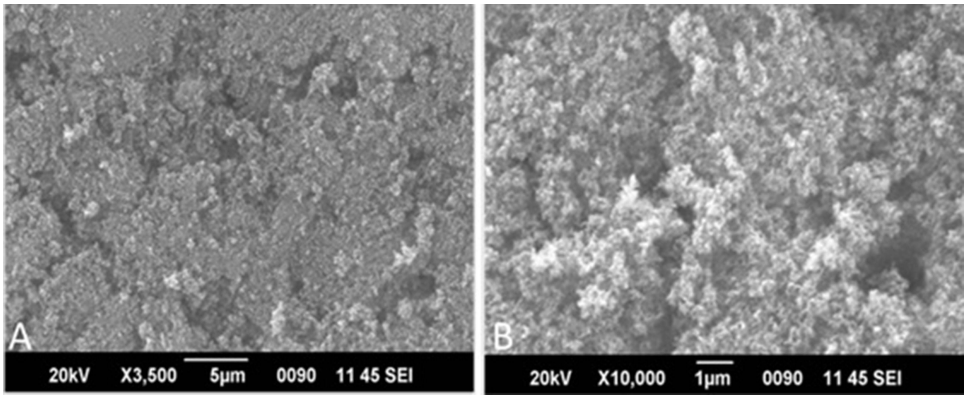

Figure 11 Scanning Electron microscopy of SDA granules at (**A**) 3500X magnification and (**B**) 10,000X magnification.

distinctive peaks (Figure 10C), which were present in the diffraction pattern of EFZ, were absent from the diffraction pattern of the SDA. Such a change in the XRD pattern implied the reduced crystallinity of the EFZ in SDA compared to that of pure EFZ. The improved dissolution of EFZ has been caused by a decrease in drug crystallinity. These findings are in good agreement with the DSC results.

SEM Analysis

Figure 11 shows the presence of an irregularly shaped crystalline agglomerate of EFZ-SDA under the SEM at different magnifications. Aerosil-200 possesses inter- and intra-specific pores on its surface that provide a much larger surface area. Such a large surface area facilitates the complete adsorption of the molten mass of EFZ SD on the porous surface of Aerosil-200.[58] The SDA did not exhibit any particle agglomeration and possessed free-flowing properties.

Evaluation of EFZ-SDA Tablets

Tablets of EFZ SDA granules were compressed using the direct compression method with a bulk equivalent to 25 mg EFZ. The tablets were also compressed from the plain EFZ powder using the direct compression method. Physical qualities (Table 6) and dissolution patterns (Figure 12) were assessed. EFZ-SDA tablets were superior to the plain EFZ tablets in terms of all physical characteristics, including thickness, hardness, and friability (Table 6). The dissolution studies were conducted using an aqueous sodium lauryl sulfate solution as a dissolution medium. The dissolution profile of plain EFZ tablets and SDA tablets using a dissolution medium of buffer (pH 3.8) showed that EFZ was released from SDA tablets faster than the plain tablets. From SDA tablets, more than 70% drug was released within 20 min, and more than 95% drug was released within 60 min. On the other hand, only 18% of the drug was released from plain tablets after

Table 6 Evaluation of SDA and Plain EFZ Tablets

Characteristics	SDA Tablets	Plain EFZ Tablets
Thickness (mm)	4.34 ± 0.11	3.8 ± 0.10
Hardness (Kg cm^{-2})	5.2 ± 0.12	4.7 ± 0.09
Friability (%)	0.79 ± 0.05	0.82 ± 0.07
Drug content (%)	95.06 ± 2.68	96.28 ± 2.54
%CDR	93.36 ± 3.41	60.14 ± 2.89

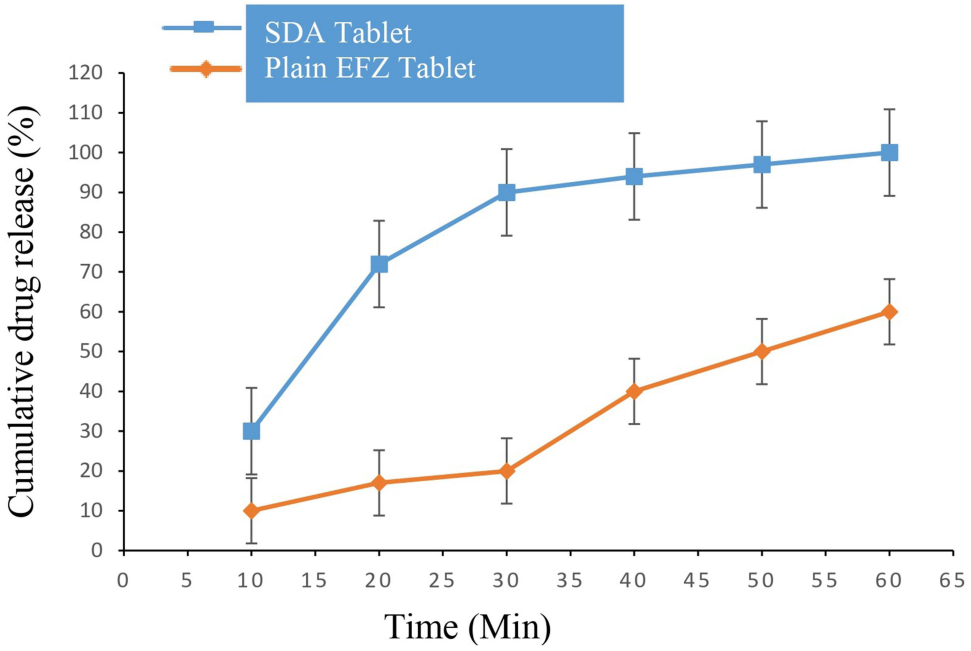

Figure 12 In-vitro dissolution study of SDA tablets and Plain EFZ tablets.

20 min, and only 62% after 60 min. The time taken for the release of 50% of the drug from the SDA tablet was only 15 min, whereas the time required for the same amount of drug release from the plain EFZ tablet was 47 min. Within 30 min, 90% of the drug was released from the SDA tablet, whereas only 22% of the drug was released from the plain EFZ tablet. The dissolution efficiency was found to be enhanced from 50.68% in the case of plain EFZ tablets to 96.18% for EFZ-SDA tablets. The improved dissolution may be caused by hydrogen bonding between the drug and carrier and adsorption on the adsorbent, which enhances wettability and decreases crystallinity of the drug.[59] The SDA technique utilized in the present study was not only able to improve the flow properties of the drug but also improve the dissolution rate of EFZ.

Stability Studies

Accelerated stability studies of EFZ-SDA at 40 ± 2°C temperature and 75 ± 5% relative humidity for 6 months were performed. The results showed no significant changes in the drug content and drug release patterns from the SDA tablets (Table 7). The results of the stability study demonstrated the efficiency of aerosil in enhancing the physical stability of the drug and preventing the transition of the drug from less crystalline to crystalline form.

Table 7 Stability Study of SDA Tablets

Evaluation Parameters	0 months	6 months
Angle of repose (°)	20.30°	21.30°
Drug content (%)	95.08	92.35
Solubility (µg/mL)	0.784	0.789
% CDR	90.35	88.99

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Conclusion

In this study, a physically stable SDA of EFZ was prepared using the hybrid technology, which is the integration of SD formulation and adsorption of SD on adsorbent carriers. The present study demonstrated the employability of the SDA hybrid technique in augmenting the dissolution rate and flow attributes of the formulation. As discussed earlier, EFZ exhibits limited oral bioavailability, which can lead to virological failure in HIV-infected patients. Thus, achieving higher bioavailability at a safe dose remains the best achievable recourse for therapeutic effectiveness. The factorial design used for the optimization of SDA suggested the ratio of 2:(2:1) of adsorbent to SD, where SD was formulated using a 2:1 ratio of PEG 6000 and EFZ, to be employed for the preparation of EFZ-SDA. The prepared SDA of EFZ at a given ratio demonstrated improved dissolution and better flow characteristics when compressed as tablets. Furthermore, the aging conditions had no impact on the physical stability and drug release of SDA. Therefore, SDA is a novel method to enhance the dissolution and flow properties of drugs. In conclusion, SDA techniques can be employed in the manufacturing of solid dosage forms of drugs with low solubility and variable bioavailability.

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Disclosure

The authors claim they have no competing interests to disclose.

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