INTRODUCTION

Oral drug delivery is the most simple, convenient, cost-effective, easiest, and non-invasive way of administration. Because of the high stability, smaller bulk, accurate dose, easy manufacturing, and repeatable in vivo plasma concentration following oral administration, the majority of novel chemical entities are designed to be operated as the solid dosage form. Solid oral dosage forms have major influence over other types of oral dosage forms. There are more promising medicine candidates available due to technological advancement, however, the majority of active pharmaceutical ingredients (APIs) with high possibility, low and alterable oral bioavailability due to their poor aqueous solubility at physiological pH and resulting decrease in dissolution rate, which causes a number of challenges when creating oral solid dosage forms. Therefore, efforts to elevate the dissolution of drugs with restricted water solubility are often needed. There has been growing interest in researchers to pivot the increase in dissolution of low water-soluble drugs for oral delivery through amelioration in solubility and control of drug release, by manufacturing the formulations more biocompatible with better bioavailability. The most important process for intestinal absorption is the solubility of the drug molecules in biological fluid. One of the major drawbacks for low absorption and high individual irregularity of drugs is the lack of solubility in physiological fluids. Solubility is one of the peripheral restrictions in drug formulation and biopharmaceutical pattern. Biopharmaceutical Classification System (BCS) classifies such drugs into two major classes according to their permeability characteristics: Class II and IV. The critical and limiting step for oral drug bioavailability, especially for BCS class II drugs is the drug release, by improving this it is possible to increase their bioavailability and decrease side effects. Therefore pharmaceutical study is mainly focused on two key areas: firstly to enhance the oral bioavailability of active agents including solubility enhancement and dissolution frequency of poorly water-soluble drugs and secondly to improve the permeability of poorly permeable drugs. Current challenges in the pharmaceutical sector are related to strategies that improve the water solubility of drugs. The methods which are commonly been used to overcome the hindrance associated with poorly water-soluble drugs, in general, includes salt formation, prodrug formation, particle size reduction, using solubilizing agent, complexation, micelles, micro-emulsions, nanoemulsions, nanosuspensions, solid–lipid nanoparticle co-precipitation, spray-drying, and freeze-drying. The Solid dispersion is the most

Keywords: Deferasirox, Polyvinyl pyrrolidone, solid dispersion, Factorial design, Solubility.
convenient technique for increasing the bioavailability and solubility of poorly water-soluble drugs. 16

To improve the overall hydrophilicity of the poorly soluble drug, a water-soluble carrier or hydrophilic polymer is chosen for the solid dispersion system. 17 The most generally been used carriers includes PVP, Tween 80, Gelucire, PEG, etc.18,19 Deferasirox (DFX) belongs to Biopharmaceutical Classification System (BCS) class II compound showing low solubility and high permeability. The critical parameter for deferasirox bioavailability is mainly its solubility. In the present work, the purpose is to create SD formulation of DFX with improved solubility. For this intend, firstly, solid dispersions of DFX were formulated using Polyvinyl pyrrolidone a polymer by accepting solvent evaporation preparation methods, and studied systematically using an optimization technique. To achieve the optimization in pharmaceutical formulations it is better to choose and combine the ingredients that will result in a formulation whose properties justify with certain preconditioned requirements. The nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis.20

To examine the impact of two formulation factors, a 3² Randomized factorial design was employed. In this design, two variables were assessed at a total of three levels for each, and experimental trials were run in all possible nine combinations. 21

### MATERIALS AND METHODS

#### Materials:

Deferasirox was procured as a gift sample from Jubilant Generics Limited, Noida. Polyvinyl pyrrolidone was bought from Merck India Ltd. (Mumbai). All chemicals used were of analytical grade.

#### Methods:

**Preparation of Deferasirox SD:**

Solid dispersions of Deferasirox in PVP containing different weight ratios (Dx: PVP 1:1, 1:3, and 1:5, respectively) were prepared by the modified solvent evaporation method.[22] To a solution of weighed quantity of deferasirox in a minimum amount of ethanol, the appropriate amount of PVP was added. The resulting mixture was agitated for 1 h and evaporated at 45–50°C on water bath until nearly dry and then stored in desiccators over anhydrous CaCl₂ to constant weight.

**FULL FACTORIAL DESIGN**

This design was adopted to optimize SD-Deferasirox formulations using the Design-Expert Software.23 In this design, the experimental trials were conducted with all the 9 possible combinations. The drug-to-polymer ratio and solvents ratio were considered as independent variables and percent yield, saturation solubility, and drug content as dependent variables. Low (−1), medium (0), and high (+1) are the values of the drug: polymer and water: ethanol respectively. All the possible batches were shown in Table 1.

#### Table 1: Experimental runs, formulation variables, measured responses of the factorial design

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Independent variable</th>
<th>Dependent variable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coded</td>
<td>Decoded</td>
</tr>
<tr>
<td>X₁</td>
<td>X₂</td>
<td>X₁' X₂'</td>
</tr>
<tr>
<td>1</td>
<td>-1</td>
<td>-1 1:1 2:8</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-1 1:2 2:8</td>
</tr>
<tr>
<td>3</td>
<td>+1</td>
<td>-1 1:3 2:8</td>
</tr>
<tr>
<td>4</td>
<td>-1</td>
<td>0 1:1 5:5</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0 1:2 5:5</td>
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<td>6</td>
<td>+1</td>
<td>0 1:3 5:5</td>
</tr>
<tr>
<td>7</td>
<td>-1</td>
<td>+1 1:1 8:2</td>
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<tr>
<td>8</td>
<td>0</td>
<td>+1 1:2 8:2</td>
</tr>
<tr>
<td>9</td>
<td>+1</td>
<td>+1 1:3 8:2</td>
</tr>
</tbody>
</table>

**EVALUATION OF DEFERASIROX SD**

#### Percentage yield:

The percentage yield is useful to regulate the efficiency of a preparation technique. The percentage yield was calculated as per the following formula.

\[
\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100
\]

#### Drug Content:

Assay of drug content of Deferasirox SD involved dissolving accurately weighed amounts of powdered SD in 100 ml of methanol and stirring on a magnetic stirrer for 10 min. It was filtered through a membrane filter (0.45 µm), and drug content was determined at 248 nm by UV-spectrophotometer.[24]

\[
\% \text{ Drug Content} = \frac{\text{Practical drug content in solid dispersion} \times 100}{\text{Theoretical drug content of solid dispersion}}
\]
Saturation Solubility Studies:
Solubility of the sample (i.e. pure Deferasirox and SD) was determined by allowing an extreme quantity of it to be dissolved in 10 ml of distilled water. The solutions were stirred in magnetic stirrer at 37 ± 0.5 °C at 50 rpm for 48 hours. The solution was then filtered through a mixed cellulose ester microfilter of 0.45 mm pore size and interpreted by UV spectrophotometer (Shimadzu Corporation, Japan) at 248 nm.

Fourier transform infrared spectroscopy studies (FTIR):
This analysis was accomplished to confirm the compatibility between pure drug and optimized formulation. The pure drug, physical mixtures, and optimized formulation were subjected to FTIR analysis by using an IR spectrophotometer equipped with an Attenuated Total Reflectance (Bruker Alpha Π ATR).[25] The samples were scanned over a range between 4000 cm⁻¹ and 600 cm⁻¹.

Differential Scanning Calorimetry (DSC):
This analysis was accomplished to determine the thermal properties and degree of crystallinity of plain Deferasirox and optimized solid dispersion of DFX. The DSC thermograms were recorded at a temperature range from 25°C to 375°C and heating rate of 10 °C/min. All samples were scanned in duplicate sets.[26]

Powder X-ray diffraction (XRD):
This analysis was used to investigate the crystallinity of pure Deferasirox and SD by using an X-ray diffractometer. Powder X-ray diffraction pattern were traced employing an X-ray diffractometer. The sample was analyzed over 2θ range of 0-50°

In vitro dissolution:
This study was conducted using USP apparatus type- 1 (Electrolab Pvt. Ltd, Goregaon, Mumbai). The specific amount of SD was add on to the dissolution media (900ml, 6.8 pH phosphate buffer) and the temperature was kept at 37 ± 0.5 °C with a stirring rate of 50 rpm. At a predetermined period of time interval, 5 ml of aliquots were isolated and filtered through a 0.45 μ membrane filter (Nunc, New Delhi, India). After suitable dilution then it was analyzed with a UV spectrophotometer (Shimadzu UV-1700) at 248 nm. The dissolution test was performed in triplicate.[27]

Release kinetics:
Various kinetic models, such as zero-order, first-order, Higuchi, Hixson Crowell, and Korsmeyer-Peppas were used to abate the drug release kinetics of SD. In model-dependant approach, release data was suitable to five kinetic models which include the zero-order, first-order, Higuchi matrix, Peppas-Korsmeyer and Hixson-Crowell release equations i.e. Eq. 1, Eq. 2, Eq. 3, Eq. 4 to find the equation with the best fit.

\[ R = k_1t \] Eq. 1

\[ \log UR = k_2t / 2.303 \] Eq. 2

\[ R = k_3 \sqrt{t} \] Eq. 3

\[ \log R = \log k_4 + n \log t \] Eq. 4

\[ (UR) 1/3 = k_5 t \] Eq. 5

Where \( R \) and \( UR \) are the released and unreleased percentages at time \( t \)

\( k_1, k_2, k_3, k_4 \) and \( k_5 \) are the rate constants

RESULTS
3^2 Factorial design:
Traditional designing methods of pharmaceutical formulations are based on the time-consuming approach of changing one variable at a time which does not come into consideration the joint effect of independent variables. Thus, factorial design can serve as an essential tool to understand the complexity of pharmaceutical formulations. In this study, a 3^2 factorial design was employed containing 2 factors estimated at 3 levels, and experimental trials were conducted for all 9 possible combinations. The formulation variables and their ranges were selected as per their preliminary studies. The independent variables are drug-to-polymer ratio and water-to-ethanol ratio and nine formulations were formulated and all the nine formulations were evaluated for percentage yield, drug content, and saturation solubility. All possible nine formulations with the evaluated results depicts in Table 1.

Selection of optimization batch:
For the selection of optimization of a batch, a multi-criteria decision approach was used. The required constraints were applied on the dependent variable such as % yield was made maximum (86.22%), drug content was made maximum (58.77%) and saturation solubility was also made maximum (0.695mg). Our intention was to keep both independent variables (X1 and X2) as the target. Hence, the solutions were given and a PO batch was found with desirability of 0.810 as shown in Table 2.

3D response surface plots and two-dimensional contour plots was taken from the data with DESIGN EXPERT software to determine the effect of the independent variable on each response as depicted in fig. 1.

Table 2: Solution of the optimization by factorial design

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug: Polymer</th>
<th>Water: Ethanol</th>
<th>%yield</th>
<th>Drug content</th>
<th>Saturation solubility</th>
<th>Desirability</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>-1</td>
<td>-0.891</td>
<td>70.991</td>
<td>57.33</td>
<td>0.651</td>
<td>0.810</td>
</tr>
</tbody>
</table>
Figure 1: 3D response surface plot and contour plots showing the effect of drug polymer ratio and solvent ratio on (a) % yield (b) drug content (c) saturation solubility

Percent yield:
According to Table 1, the percentage yield obtained by formulating all nine formulations ranged from 58.58% to 86.22%.

Saturation solubility:
In distilled water, the saturation solubilities of pure DFX and DFX-SD were determined. The saturated solubility of DFX was determined to be 61.726 μg/ml, while SD-DFX was determined to be 612.0 μg/ml. When compared to DFX, the saturated solubility of DFX-SD was significantly higher (up to a 10-fold increase).

Drug content:
All nine made formulations had a drug content that varied from 28.58% to 58.77%. The F7 batch contained the most drug of any formulation.

Fourier Transform Infrared (FTIR):
The potential physicochemical relationship between Deferasirox and PVP was researched using FT-IR. The infrared profile of SDs frequently undergoes discernible alterations due to the drug and carrier interaction. Fig 2 shows the FT-IR spectra of DFX, PVP, their physical mixture, and solid dispersion. The carbonyl group's distinctive absorption bands at 1677.73 cm⁻¹, the C=C stretching vibration's at 1607.40 cm⁻¹, the C≡N group's at 1352.72 cm⁻¹, the C-H stretching vibration's at 3019.44 cm⁻¹, and the N-H stretching vibration's at 3314.50 cm⁻¹ were all clearly visible in the Deferasirox FT-IR spectra. PVP displayed a C=O stretching vibration at 1648.50 cm⁻¹, C≡N stretching vibration at 1286.18 cm⁻¹, C-H stretching vibration at 2739.43 cm⁻¹, O-H stretching vibration at 3253.52 cm⁻¹, N-H stretching vibration of 1st & 2nd amine at 3400.67 cm⁻¹ and 3306.59 cm⁻¹. The distinctive band for the physical mixture can be seen at the frequencies of C=O stretching vibration at 1679.60 cm⁻¹, C≡C stretching vibration at 2116.9 cm⁻¹, and O-H stretching vibration at 3295.0 cm⁻¹.
at 1607.90 cm⁻¹, and CN group at 1352.29 cm⁻¹. Solid dispersion exhibits C=O stretching vibrations at 1663.72 cm⁻¹, C=O stretching vibration at 1608.66 cm⁻¹, C-H stretching vibrations at 2884.86 cm⁻¹, and O-H stretching vibrations at 3415 cm⁻¹. There was no interaction between Deferasirox and PVP in the physical combination, as evidenced by the bands of the drug also being present in the physical mixture’s FT-IR spectrum. In comparison, the FT-IR spectrum of solid dispersion showed the absorption band attributed to O-H stretching vibration. It might be the outcome of hydrogen bonding developing between Deferasirox and PVP. This FT-IR study showed the hydrogen bonding interaction between Deferasirox and PVP in solid dispersion altered Deferasirox crystalline structure.

Figure 2: FT-IR spectra of (a) Deferasirox (b) PVP (c) Physical mixture (d) solid dispersion

In-vitro dissolution:
The DFX-in-vitro SD’s drug dissolution patterns are displayed in fig 3. According to the findings, Deferasirox’s rate of dissolution in solid dispersion was considerably higher than it was for plain Deferasirox. The free Deferasirox only got up to 9.87% after 60 minutes, which was roughly 7 times less than the release behaviour SD of the DFX formulation. In contrast, the amount of drug released from the optimised DFX-SD formulation was up to 72.16%. It was discovered that increasing the carrier proportion in the formulation resulted in a noticeable boost in dissolution. The interfacial tension between the drug and the dissolution medium was thought to be decreased through the reduction of particle size, increase in surface area, transition to the amorphous state, and increase in wettability and dispersibility in order to achieve a better release behaviour. With a rise in polymer concentration, the release values demonstrated Deferasirox’s improved ability to dissolve in SD.
Drug Release Kinetics and mechanism:

Release data were analysed in accordance with various kinetic equations to characterise the kinetics of drug release from SD matrix tablets. The data were examined using the regression coefficient technique, and Table 3 displays the regression coefficient value ($r^2$) for each batch.

On analyzing regression coefficient values of all batches, it was found that formulation F1 followed Hixon–crowelk release kinetics, F2, and F4 exhibit first-order release kinetics, F3 F8, and F9 showed matrix release kinetic, F5 followed Zero order release kinetic, and F6, F7 exhibit Peppas release kinetic.

First order could be used to describe the in-vitro release profiles of drugs from SD the best because the plots displayed the highest linearity. The data were fitted into the Korsmeyer-Peppas equation to corroborate the diffusion mechanism. The formulations showed good linearity with slope ($n$) between 0.515 and 0.993, which seems to suggest coupling of the diffusion and erosion mechanisms, also known as anomalous diffusion.

### Table 3: In vitro Release Kinetics Parameters of Deferasirox

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Hixon-crowell</th>
<th>Korsmeyer-peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>$k$</td>
<td>$r^2$</td>
<td>$k$</td>
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<tr>
<td>F2</td>
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<td>0.7291</td>
<td>0.9898</td>
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<td>0.9798</td>
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<tr>
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<td>0.5848</td>
<td>0.9467</td>
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<tr>
<td>F4</td>
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<td>0.9952</td>
<td>-0.0213</td>
<td>0.9799</td>
</tr>
<tr>
<td>F5</td>
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<td>0.9699</td>
<td>0.9129</td>
<td>-0.0136</td>
<td>0.9136</td>
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<tr>
<td>F6</td>
<td>0.9642</td>
<td>0.4774</td>
<td>0.9773</td>
<td>-0.0054</td>
<td>0.9834</td>
</tr>
<tr>
<td>F7</td>
<td>0.9816</td>
<td>1.0974</td>
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<td>-0.0157</td>
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<tr>
<td>F8</td>
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<tr>
<td>F9</td>
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<td>0.4785</td>
<td>0.9530</td>
<td>-0.0054</td>
<td>0.9787</td>
</tr>
</tbody>
</table>

Differential Scanning Calorimetry (DSC):

The thermal characteristics and level of crystallinity of the synthesized DFX-SD were evaluated using DSC. As depicted in fig. 4. The DSC curve for DFX shows a single endothermic reaction that corresponds to the drug melting. The onset of melting was observed at 264.17°C while thermograms of SD showed the absence of a DFX melting peak but the presence of an exothermic peak at 75.24°C and 217.36°C. Strong evidence that DFX was completely soluble in the liquid phase of the polymer or the lack of a crystalline form of DFX, which is favourable to rapid bioavailability during in vivo drug release, was the disappearance of a DFX endothermic peak and the presence of an exothermic peak in solid dispersion.
Figure 4: DSC diffractogram of (a) DFX (b) SD

**Powder X-ray diffraction (XRD):**

Crystallinity was further confirmed by comparing some representative peak heights in the diffraction of the solid dispersion with those of the DFX as shown in Fig 5. DFX showed the sharp peak of the diffraction angle of 2θ at 10°, 14°, and 26° with peak intensities of 271.2, 270.64, and 251 respectively revealing its crystalline nature. The Diffractogram of the solid dispersion showed fewer, broader, and less intense peak with the same diffraction angle of 2θ (10°, 14°, 26°) with peak intensities of 198.77°, 232°, 216°. The Diffractogram of the optimized system showed a prominent reduction and diminished intensity of DFX corresponding peaks reflecting its amorphous existence in the optimized system. The drug being trapped within the incorporated polymer is thought to be the cause of the observed decrease in peak strength, which further supports DFX amorphization.

Figure 5: XRD diffractogram of (a) DFX (b) SD

### DISCUSSION

The goal of the current research is to prepare and assess SD of DFX in PVP for improving the solubility of the BCS class drug Deferasirox. Utilizing the solvent evaporation method, DFX-SD formulation was produced as a pure drug in PVP using the following ratios drug: carrier in 1:1, 1:2, 1:3 and water: ethanol in 2:8, 5:5, 8:2. DFX-SD formulation was optimized as per 3² randomized factorial design by solvent evaporation method with a view to evaluating the effect on %yield, drug content, and saturation solubility. For this purpose, 3 level of DFX to PVP ratio (1:1, 1:2, 1:3) and water to ethanol ratio (2:8, 5:5, 8:2) were selected and are involved in 3² factorial study. All the solid dispersions prepared were found to be fine and free-flowing powders. The percent drug content indicated uniformity of drug content in each batch of solid dispersion prepared. High production yields varying from 58.58% to 86.22% are present in all of the prepared formulations. The F1 had the greatest drug content, with a drug to polymer ratio of 1:1 and a solvent ratio of 2:8. The F8 compound, where the solvent to polymer ratio is 8:2 and the polymer concentration is double, produced the greatest yield. In contrast to F4, which
demonstrated the highest saturation solubility of 0.695 mg/ml, the pure drug’s saturation solubility is 0.0617 mg/ml, a 10-fold rise.

For batch optimization, a multi-criteria decision-making approach was used. The following constraints were applied: %yield is maximum i.e. 86.22%, drug content is maximum up to 58.77%, and saturation solubility is maximum up to 0.695mg/ml. To obtain an effective formulation, both of the independent variables were set to their desired value. The solution obtained after optimization was the drug: polymer ratio was 1:1 & the solvent ratio 2:8 and the optimized response was a %yield to be 70.99%, drug content to be 57.83%, and saturation solubility to be 0.691mg/ml. The improvement was discovered to be 0.810 percent desirable. The checkpoint batch was prepared and evaluated with similar results.

In-vitro dissolution tests of various DFX formulations made using the solvent evaporation technique revealed that the DFX-SD made using this technique displayed improved dissolution rate as the effective surface area over which the drug distributes increases along with an improvement in drug dissolution. The saturation solubility in the solid dispersion samples rises as PVP levels rise. Because PVP is a hydrophilic polymer, it makes the surface of hydrophobic drug particles more hydrophilic, improving their wettability for increased absorption.

Additionally, amorphous solid dispersion matrices were created from DFX molecules that were present in the amorphous condition in the PVP-containing SD samples. Amorphous solid dispersion systems have demonstrated higher saturation solubility in comparison to pure drug systems or their physical mixtures in a number of prior investigations. In spite of being present in the amorphous state in these samples, Deferasirox in this instance interacts with PVP through hydrogen bonding to create a consistent solid dispersion matrix. Due to PVP’s hydrophilicity, this condition causes Deferasirox molecules to hydrate more quickly, leading to the observed improvement in solubility. Additionally, the PVP in these samples has Deferasirox molecules distributed throughout the matrix. The carrier (PVP) is appropriate for the solid dispersion of Deferasirox because it has been determined from the IR studies that the drug and polymer used interact physically, such as through hydrogen bonds, with no chemical change. The optimized batch was further studied for DSC and XRD studies which indicated that Deferasirox lost their crystalline structure presenting an amorphous porous structure. The goal was accomplished, and these results indicated that the aforementioned technique could be successfully used to increase the solubility of drugs that aren’t very water soluble.

CONCLUSION

Solid dispersion (SD) exhibits a superior dissolution profile when compared to a poorly water-soluble drug administered alone in terms of drug release, dissolution effectiveness, and dissolution rate. Different stoichiometric ratios of Deferasirox and PVP as a carrier were used in this research to create SDs using the solvent evaporation method. The findings of the experimental study demonstrate that the drug-to-carrier ratio and solvent ratio have a substantial impact on the dependent variable, which includes yield percentage, drug content, and saturation solubility. The impact of the independent dependent variable was evaluated using a response surface map. Due to the presence of an amorphous form of Deferasirox, which was verified by FT-IR, DSC, and XRD studies, and to a reduction in particle size during the formation of solid dispersion, which allows for good wettability of particles in dissolution, the drug’s improved solubility may have improved. The use of experimental design methods for formulation optimization allowed for the quickest possible arrival at the optimal point with the least amount of effort. Therefore, it can be inferred that one of the alternative techniques for increasing the solubility of the inadequately water-soluble drug Deferasirox is the solid dispersion approach.

Conflict of Interest

The authors affirm that they have no known financial or interpersonal conflicts that might have looked to have an impact on the research presented in this paper.

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