FORMULATION AND IN-VITRO EVALUATION OF DEFERASIROX SPRINKLE GRANULES AND DEFERASIROX FILM COATED TABLETS WITH IMPROVED ORAL BIOAVAILABILITY

Natha Vani Latha, D.Venkataramana, J.Pravalika*
Department of Pharmaceutics, Holy Mary Institute of Technology and Science, Keesara, Bogaram, Ghatkesar Rd, Kondapur, Telangana, 501301.

ABSTRACT: ***To enhance the solubility and dissolution rate of Deferasirox by solid dispersion method (Solvent evaporation) using polyethylene glycol (PEG 6000) and poloxamer 188.To prepare tablets of optimized batch (MF_9). Evaluations: The prepared Deferasirox solid dispersion was characterized in terms of drug content, solubility, and dissolution studies, Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), and X-ray diffraction (XRD). The prepared optimized solid dispersion Deferasirox tablets were evaluated for hardness, friability, drug content, and dissolution study. Results: The FTIR spectra showed no significant change in the chemical nature. The DSC confirms to preparation of solid dispersion. The X-ray diffraction showed a decrease in crystalinity. The X-ray diffraction (XRD) of optimized solid dispersion after stability showed no significant change in crystalinity that was the same as before stability. The aqueous solubility and dissolution rate of Deferasirox tablets was significantly increased. Conclusion: The prepared tablets of Deferasirox showed more solubility and in-vitro drug release compared to a marketed tablet.***
Keywords: Deferasirox, PEG 6000, poloxamer 188, Solid dispersion, Tablet.

I. INTRODUCTION

Oral dosage forms have many advantages like accurate dosage, less bulk, greater stability, and easy production is possible. At present, to the formulation scientists in the pharmaceutical industry one of the most major challenges is the formulation of poorly soluble compounds for oral delivery.[1] Poor aqueous solubility can lead to failure in the formulation development process. The main reason behind inadequate bioavailability of the drug is its low dissolution rate and low solubility in an aqueous medium.[2] Nowadays, most of the drug substances are innovated but the venture to improve the solubility and dissolution of hydrophobic drug substances remains one of the trickiest tasks in drug development. Dissolution of the drug in aqueous medium like gastric fluid is important to get better absorption and bioavailability for orally administered drugs. Therefore, to progress the bioavailability of poorly water-soluble compounds like biopharmaceutical classification system class II and IV drugs, the polymer matrix of various origins can be used. Various solubility enhancement methods have been introduced to triumph over this problem. [3]Solid dispersion (including amorphous) is one useful method for improving dissolution and has been investigated as a manufacturing method for solid preparations. Deferasirox is 4-[(3Z, 5E)-3, 5-bis (6-oxo-1-cyclohexa-2, 4 dienylidene)-1,2,4-triazolidin-1-yl]benzoic acid. Deferasirox is an oral iron chelator. Its main use is to reduce chronic iron overload in patients who are receiving long-term blood transfusions for conditions such as beta-thalassemia and other chronic anaemia.

II. MATERIALS

Deferasirox was obtained from Hetero Labs, HYD. PEG6000, and Poloxamer 188 were procured from Synpharma Research Labs, Hyderabad, and other chemicals the reagents used were of analytical grade.

METHODOLOGY

FTIR Studies[5]

The solid-state interaction between Deferasirox molecules and polymers has also been evaluated using Fourier transform infrared spectroscopy (FTIR). Observable shifts in the mixture's infrared (IR) profile are a common

result of the drug's chemical interaction with the polymer. But some of the shifts are so little that the spectrum needs special attention to make sense of them.

DIFFERENTIAL SCANNING CALORIMETER[6]

DSC IS A METHOD FOR DETERMINING THE HEAT CHANGE THAT OCCURS AS A CONSEQUENCE OF CHEMICAL OR PHYSICAL REACTIONS INSIDE A SAMPLE. USING DSC, ONE MAY EXAMINE THE EFFECTS OF AN INTERACTION BETWEEN A MEDICATION AND A POLYMER ON THE MIXTURE'S CHARACTERISTICS. TESTING FOR HEAT DEGRADATION, PURITY, POLYMORPHISM, SALVATION, AND DRUG-EXCIPIENT COMPATIBILITY ARE FURTHER RELEVANT APPLICATIONS.

X-RAY POWDER DIFFRACTION[7] ONE ESSENTIAL METHOD FOR PROVING THAT A CRYSTALLINE SHAPE MAY BE RELIABLY REPRODUCED FROM BATCH TO BATCH IS X-RAY POWDER DIFFRACTION. USING THIS METHOD, THE SHAPE OF CRYSTALS IN A SOLID DISPERSION MAY BE IDENTIFIED. A PATTERN CANNOT BE GENERATED BY AN AMORPHOUS STRUCTURE. A REPEATABLE PATTERN OF PEAK INTENSITIES AT VARIOUS ANGLES (2Θ) RELATIVE TO THE INCOMING BEAM ISSEEN IN THE X-RAY SCATTERING. DIFFERENT CRYSTALLINE LATTICES EXHIBIT DIFFERENT DIFFRACTION PATTERNS FOR THE SAME CHEMICAL.

METHOD OF PREPARATION SOLID DISPERSION [8]

Using techniques such as physical mixing, solvent evaporation, and melting, Deferasirox solid dispersion with PEG6000 and Poloxamer 188 was synthesized in ratios of 1:0.5, 1:0.75, and 1:1.

Solvent evaporation method

To achieve a transparent solution, dissolve the drug and polymer in chloroform: acetone. We dried the leftovers under a vacuum for three hours and then kept them in desiccators for the night after evaporating the solvent at 40°C in a water bath while stirring continuously. The dehydrated material was mashed using a mortar, then put through a #40 sieve and kept in a desiccator until needed.

Composition of trail batches:

Table-1: Composition of Deferasirox immediate release tablets by solvent evaporation method.

Ingredients	with PEG 6000			with Poloxamer			with PEG 6000+ Poloxamer 188		
	SF_1	SF_2	SF_3	SF_4	SF_5	SF_6	SF_7	SF_8	SF_9
Deferasirox	100	100	100	100	100	100	100	100	100
MCC	100	75	50	100	75	50	100	75	50
Maize starch	20	20	20	20	20	20	20	20	20
Poloxamer188	-	-	-	50	75	100	25	37.5	50
PEG 6000	50	75	100	-	-	-	25	37.5	50
CCS	5	5	5	5	5	5	5	5	5
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of Deferasirox trial batches:

Thickness:[9]

The thickness and diameter of the formulated tablets were measured by using Vernier calipers.

Weightvariation[10]

The formulated tablets were tested for weight uniformity. 20 tablets were collectively and individually. From the collective weight, the average weight was calculated. Each tablet's weight was then compared with the average weight to ascertain whether it is within permissible limits or not.

$$\% \text{ Weight variation} = \frac{\text{Average weight} - \text{individual weight}}{\text{Average weight}} \text{ X100}$$

Hardness[11]:

The tablets crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

Friability[12]:

The Roche friability test apparatus was used to determine the friability of the tablets. 25 pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability calculated was using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X100}$$

Drugcontent[13]:

Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of Deferasirox, to a suitable volumetric flask and add an appropriate quantity of Internal standard solution Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg of USP Deferasirox RS and 0.04 mg of the internal standard per mL. Pass a portion of this solution through a membrane filter having a 0.5-µm or finer porosity, and use the filtrate.

Solubilitystudies[14]:

A solubility study was performed according to the method reported by Higuchi and Connors. Excess (usually more than 1mg/ml concentration) of solid dispersions were added to 30ml distilled water taken in stopper conical flasks and the mixture were shaken for 24hrs in a rotary flask shaker. After shaking to achieve equilibrium, 1ml aliquots were withdrawn at 1hr intervals and filtered through Whatmann filter paper. Dilute with water up to 10 ml to get 100mcg/ml solution.

From that withdrawn 1 ml solution and dilute with water upto 2.0 ml to get 20 mcg/ml solution. Analyzed by UV-spectrophotometer at 248 nm. Shaking was continued until three consecutive readings were same.

Invitro dissolution studies[15]:

In vitro dissolution studies were carried out in 900 ml of purified water+0.3% SLS using USP dissolution testing apparatus (Model TDT 08L,Electro lab, Mumbai India) with temperature of dissolution medium maintained at 37± 0.5°C.5ml of aliquots were withdrawn at regular intervals , filtered and same amount of fresh dissolution medium was replaced at the same temperature . The filtered solutions were analyzed by using (Shimadzu, Japan) UV-spectrophotometer at 257 nm.

Stability study[16]**:**

It is important to assess the effect of temperature and humidity on the stability of drug .It helps to generate information for predicting the shelf life of the product and recommended storage conditions. Stability data is required to be submitted as the part of the dossier submitted to the regulatory agencies. The major disadvantages of solid dispersion are related to their instability. Solid dispersions are very prone to conversion of amorphous form in to crystal form. Optimized solid dispersion along with its final tablet formulation was charged for the accelerated stability studies as per ICH guidelines (40 ± 2 °C and75 ± 5% RH) for a period of 1 month in a stability chamber. The samples were placed in vials with bromo butyl rubber plugs and sealed with aluminium caps. The samples were evaluated for in vitro drug release.

III. RESULTS AND DISCUSSION

SATURATION SOLUBILTY STUDY

Table-2: Solubility study

Media	Conc.(mg/ml)	With 0.2%SLS (mg/ml)	With 0.3%SLS (mg/ml)
0.1N HCL	0.010±0.0017	0.010±0.0012	0.025±0.001
Acetate buffer pH 4.5	0.010±0.0025	0.015±0.0021	0.030±0.0024
pH 3.0 buffer	0.009±0.00015	0.013±0.0024	0.027±0.0023
Phosphate buffer 6.8	0.009±0.00013	0.014±0.0011	0.029±0.0017
Phosphate buffer 7.5	0.0090±0.00015	0.015±0.00023	0.030±0.0015
Water	0.0100±0.0023	0.016±0.001	0.032±0.0016

The highest solubility of Deferasirox was observed in purified water with 0.3%SLS as compare to another dissolution media. Hence, it was concluded that purified water+0.3% SLS is best dissolution media for Deferasirox dissolution study.

Drug –Excipient compatibility study

FTIR Spectra of Deferasirox:

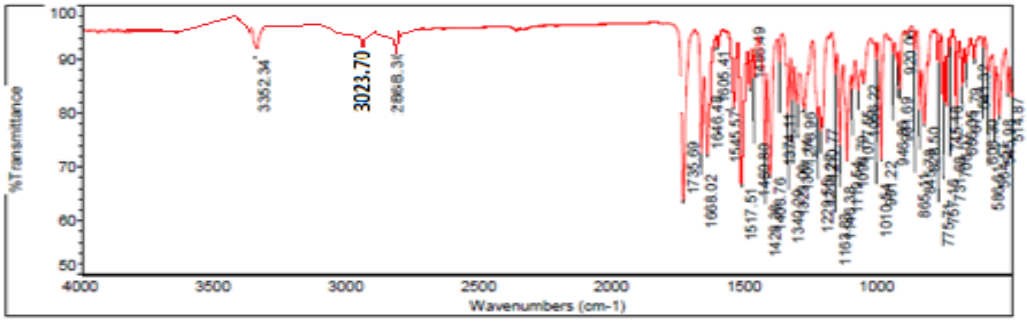

Fig.1. FTIR Spectra of Deferasirox

Differential scanning calorimetry:

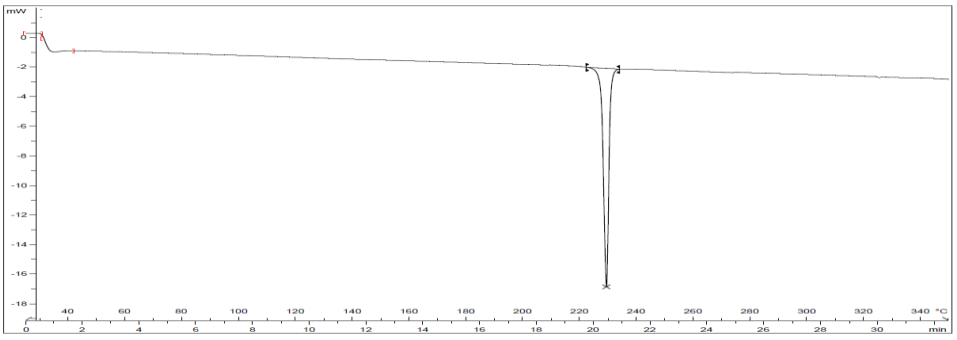

Fig.2. DSC of Pure drug Deferasirox

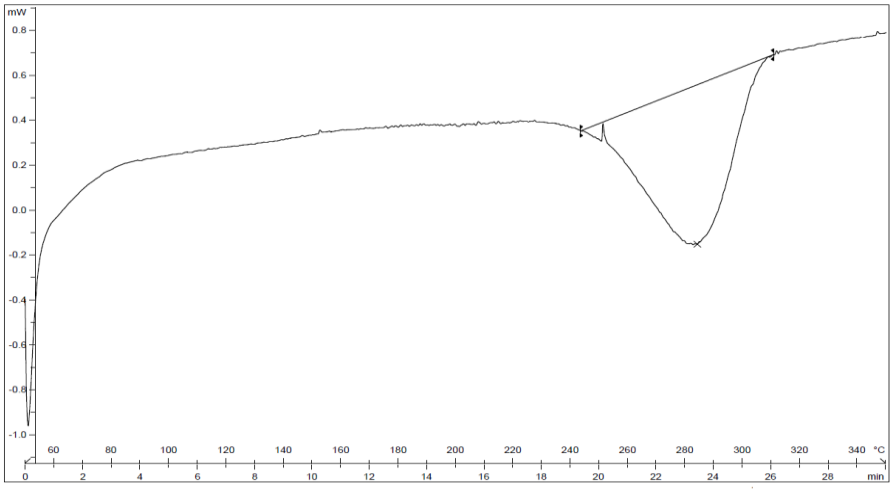

Fig.3. DSC of optimized Solid dispersion

DSC was employed to evaluate the phase transformation of Deferasirox during formation of solid dispersions. As shown in figure no 6.9 the pure drug (Deferasirox)characterized by single endothermic peak at 230°c confirming of Deferasirox. The Optimized solid dispersion formulation did not showed any sharp peak of Deferasirox suggesting the complete conversion of Deferasirox into dispersed amorphous form.

X-RAY POWDER DIFFRACTION

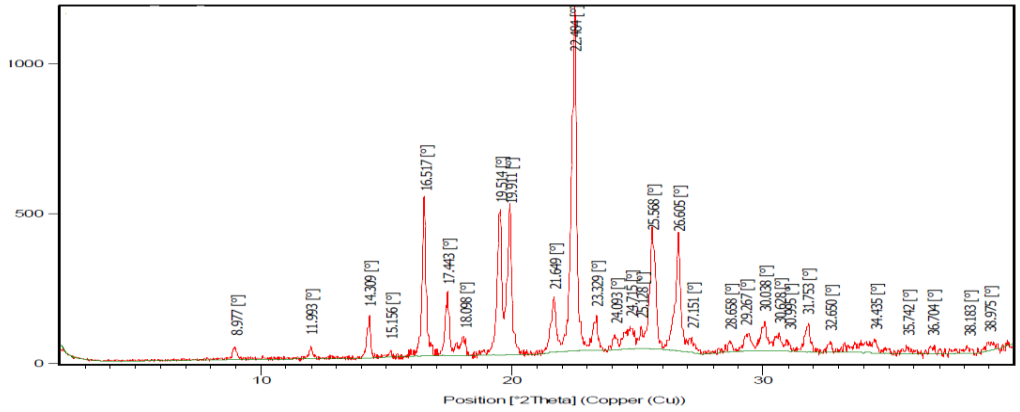

Fig.4. XRD of pure drug Deferasirox

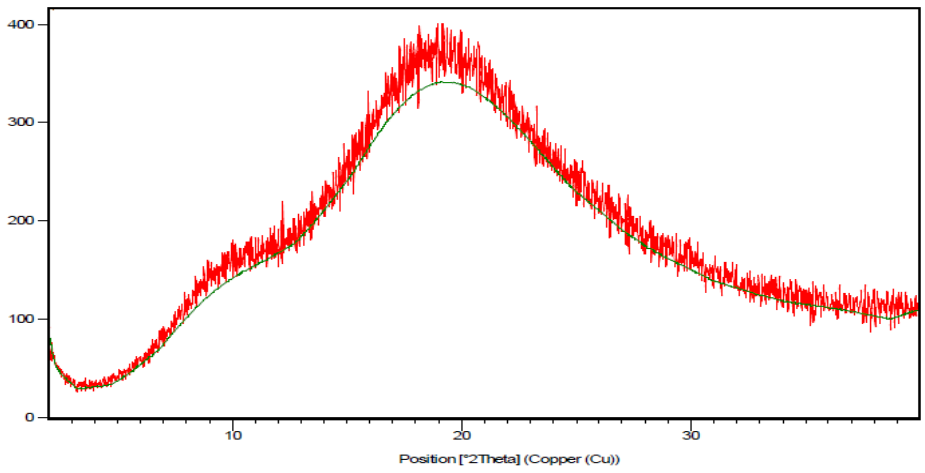

Fig.5. XRD of optimized solid dispersion

In order to further examine the physical form of drug in solid dispersion Deferasirox and optimized solid

dispersion formulation subjected to X-ray diffraction (XRD) investigation. Thediffractogram it's crystalline nature as indicated by various peaks. On other hand the diffractogram of solid dispersion showed a typical diffuse pattern with complete absence of the distinctive peaks of Deferasirox indicating amorphous nature in solid dispersion.

EVALUATION OF DEFERASIROX TABLETS

EVALUATION OF DEFERASIROX TABLETS BY SOLVENT EVAPORATION

Table-3: Evaluation of Deferasirox tablets by Solvent Evaporation

Formulations	Thickness (mm)	Weight Variation (%)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
SF1	4.4±0.43	1.75±0.42	5.5±0.26	0.46±0.02	97.6±0.35
SF2	4.5±0.22	1.48±0.33	5.8±0.13	0.33±0.03	93.7±0.27
SF3	4.6±0.35	1.57±0.47	5.7±0.11	0.55±0.01	92.7±0.31
SF4	4.6±0.17	1.47±0.28	5.9±0.37	0.75±0.04	96.8±0.15
SF5	4.7±0.21	1.99±0.26	5.6±0.14	0.47±0.03	97.6±0.13
SF6	4.5±0.42	1.92±0.24	5.5±0.31	0.63±0.02	98.9±0.37
SF7	4.5±0.33	1.85±0.13	5.9±0.27	0.37±0.04	95.7±0.32
SF8	4.6±0.25	1.67±0.34	5.7±0.41	0.46±0.06	97.5±0.28
SF9	4.7±0.41	1.43±0.46	5.3±0.46	0.34±0.01	96.7±0.26

INVITRO DISSOLUTION DATA OF DEFERASIROX TABLETS FORMULATED BY SOLVENT EVAPORATION

Table-4: Invitro dissolution data of Deferasirox tablets formulated with PEG 6000 by solvent evaporation

S.NO	Time(min)	% Drug release		
		SF_1	**SF_2**	**SF_3**
1	0	0	0	0
2	5	27.4±0.45	29.3±0.22	32.6±0.38
3	10	35.7±0.33	37.8±0.13	45.4±0.41
4	15	41.5±0.25	49.1±0.43	53.7±0.53
5	20	50.9±0.18	59.9±0.35	61.5±0.24
6	25	58.7±0.26	68.7±0.32	75.8±0.37
7	30	71.1±0.48	76.7±0.53	81.7±0.33
8	35	79.6±0.38	81.5±0.24	88.5±0.25
9	40	87.4±0.41	87.8±0.37	97.5±0.25

10	45	92.7±0.32	94.8±0.37	-

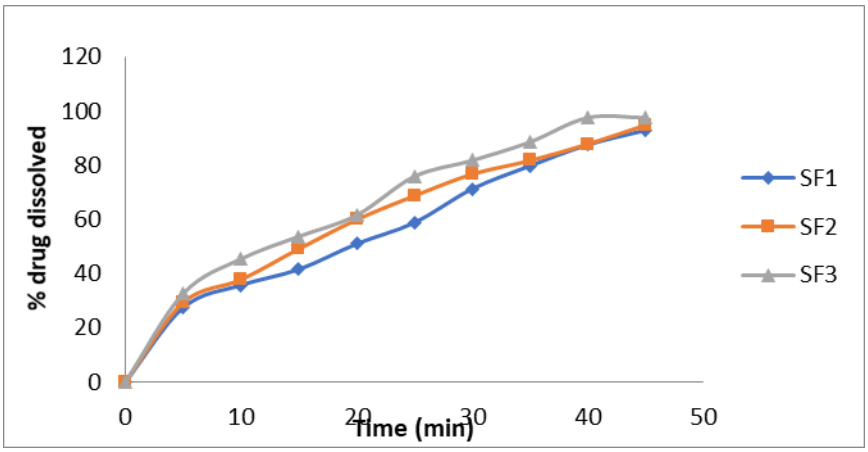

Fig.6. Invitro dissolution data of Deferasirox tablets formulated with peg 6000 by solvent evaporation

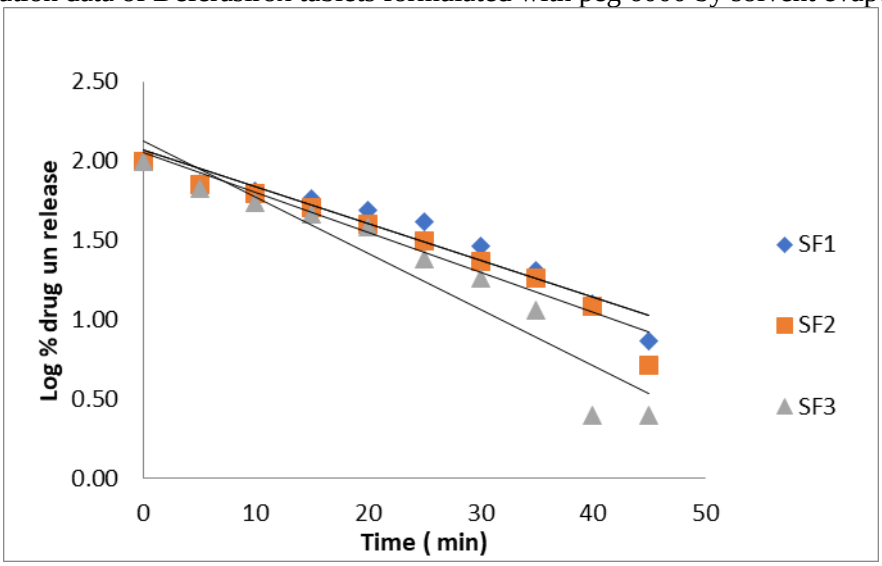

Fig.7. First order plots of invitro dissolution data of Deferasirox tablets formulated with peg 6000 by solvent evaporation

INVITRO DISSOLUTION DATA OF DEFERASIROX TABLETS FORMULATED WITH CROSPOVIDONE BY SOLVENT EVAPORATION

Table-5: Invitro Dissolution data of Deferasirox tablets formulated with Crospovidone by 45Solvent Evaporation

S.NO	Time(min)	% Drug release		
		SF_4	SF_5	SF_6
1	0	0	0	0
2	5	25.2±0.61	32.9±0.52	37.1±0.34
3	10	33.9±0.35	41.2±0.34	45.6±0.26
4	15	41.5±0.43	49.7±0.26	83.3±0.51
5	20	53.6±0.16	55.1±0.41	58.9±0.37
6	25	59.7±0.36	63.6±0.15	69.6±0.24

7	30	64.2±0.34	69.2±0.61	75.7±0.37
8	35	69.7±0.26	74.9±0.35	81.6±0.16
9	40	74.1±0.41	80.5±0.43	89.7±0.36
10	45	81.6±0.15	87.6±0.16	97.7±0.26
11	50	89.6±0.15	94.2±0.34	-
12	55	93.2±0.34	-	-

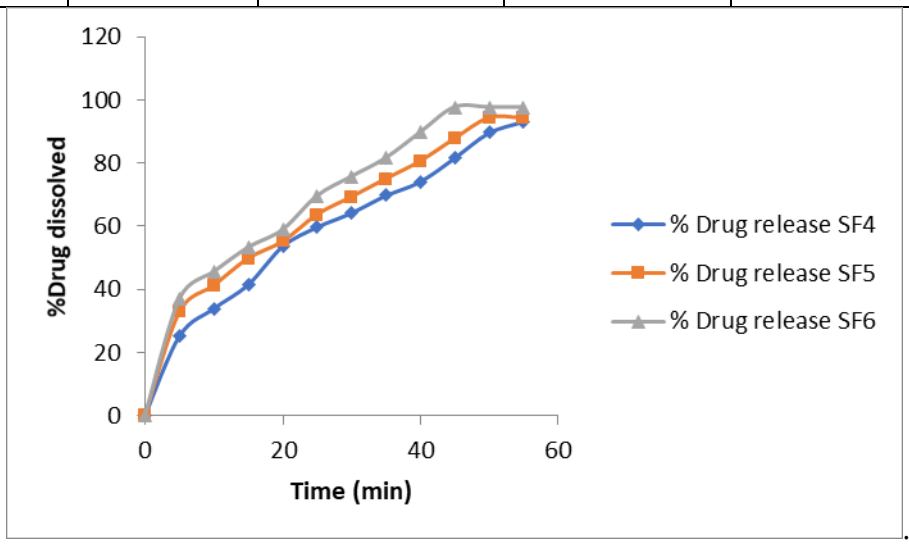

Fig.8. Invitro dissolution data of Deferasirox tablets formulated with Crospovidone by solvent evaporation

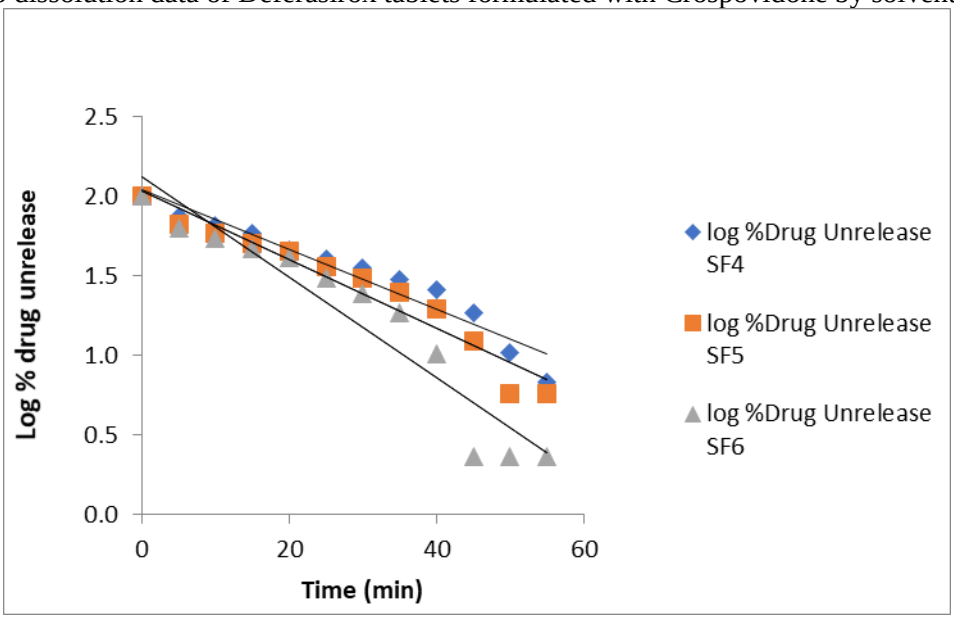

Fig. 9.First order plots of invitro dissolution data of Deferasirox tablets formulated with Crospovidone by solvent evaporation

INVITRO DISSOLUTION DATA OF DEFERASIROX TABLETS FORMULATED WITH PEG 6000 & CROSPOVIDONE BY SOLVENT EVAPORATION

Table-6: Invitro Dissolution data of Deferasirox tablets formulated with PEG 6000 &Crospovidone by Solvent Evaporation

S.NO	Time(min)	% Drug release		
		SF_7	SF_8	SF_9

1	0	0	0	0
2	5	32.4±0.45	34.3±0.22	36.6±0.38
3	10	44.7±0.33	47.8±0.13	49.4±0.41
4	15	49.5±0.25	55.1±0.43	58.7±0.53
5	20	53.9±0.18	61.9±0.35	67.5±0.24
6	25	64.7±0.26	68.7±0.32	74.8±0.37
7	30	75.1±0.48	77.7±0.53	86.7±0.33
8	35	82.6±0.38	86.5±0.24	97.5±0.25
9	40	93.4±0.41	95.8±0.37	-

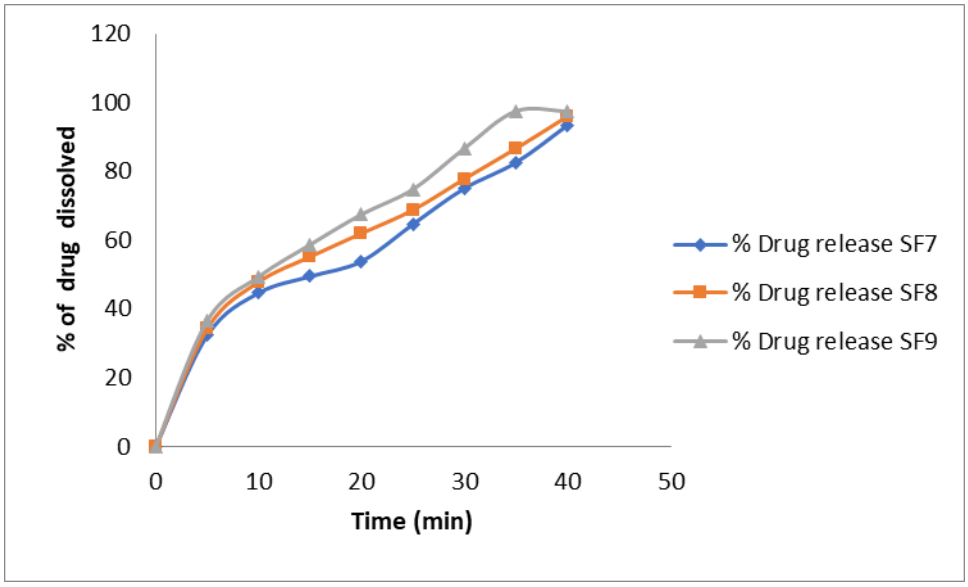

Fig.9. Invitro dissolution data of Deferasirox tablets formulated with peg 6000 & Crospovidone by solvent evaporation

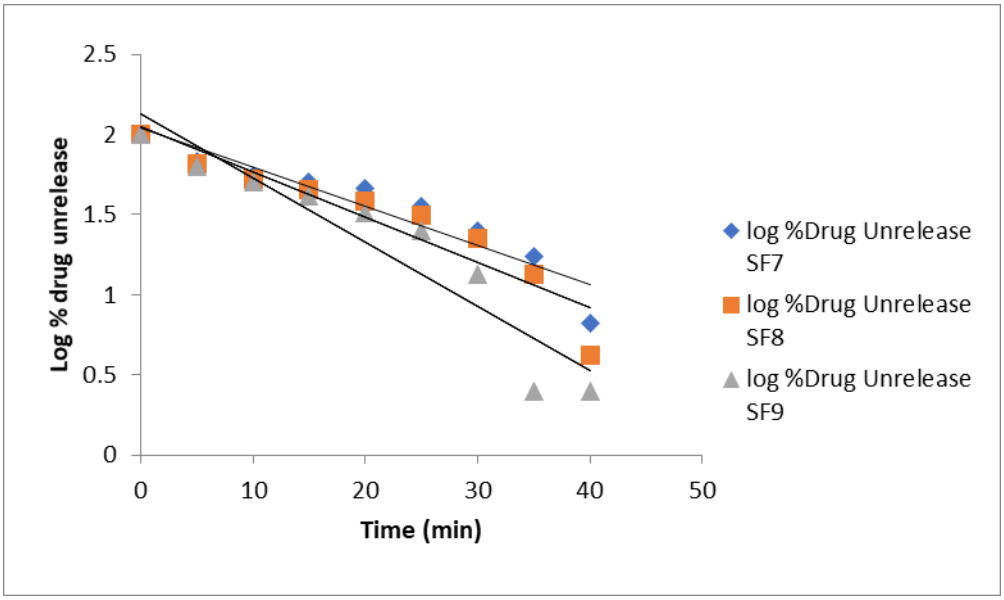

Fig.10. First order plots of invitro dissolution data of Deferasirox tablets formulated with peg 6000 & Crospovidone by solvent evaporation

IN-VITRO DRUG RELEASE KINETICS OF DEFERASIROX TABLETS FORMULATED WITH PEG 6000 & CROSPOVIDONE BY SOLVENT EVAPORATION

Table-7: In-vitro Drug release kinetics of Deferasirox tablets formulated with PEG 6000 &Crospovidone by Solvent Evaporation

Formulation	Correlation coefficient values		Release rate constant (K)(min^{-1})	T_{50} (min)	T_{90} (min)
	Zero order	First order			
SF_1	0.918	0.933	0.053	13.08	43.48
SF_2	0.855	0.945	0.058	12.04	40.00
SF_3	0.848	0.872	0.076	9.12	30.30
SF_4	0.851	0.938	0.041	16.72	55.56
SF_5	0.749	0.940	0.050	14.00	46.51
SF_6	0.702	0.906	0.071	9.71	32.26
SF_7	0.842	0.891	0.055	12.54	41.67
SF_8	0.799	0.881	0.064	10.75	35.71
SF_9	0.800	0.928	0.085	8.13	27.03

Dissolution profile of marketed tablet and solid dispersion tablet

Table-8: Dissolution profile of marketed tablet and solid dispersion tablet

Time (min)	% Drug release	
	Marketed tablet (Pletal)	Solid dispersion tablet

0	0.00	0.00
5	25±0.62	46.1±0.34
10	39±0.47	67.8±0.12
15	47±0.61	76.9±0.43
20	59±0.74	85.3±0.26
25	67±0.82	97.2±0.35
30	78±0.65	-
40	89±0.81	-
60	95.74±0.72	-

Release order of dissolution profiles of marketed tablet and solid dispersion tablet:

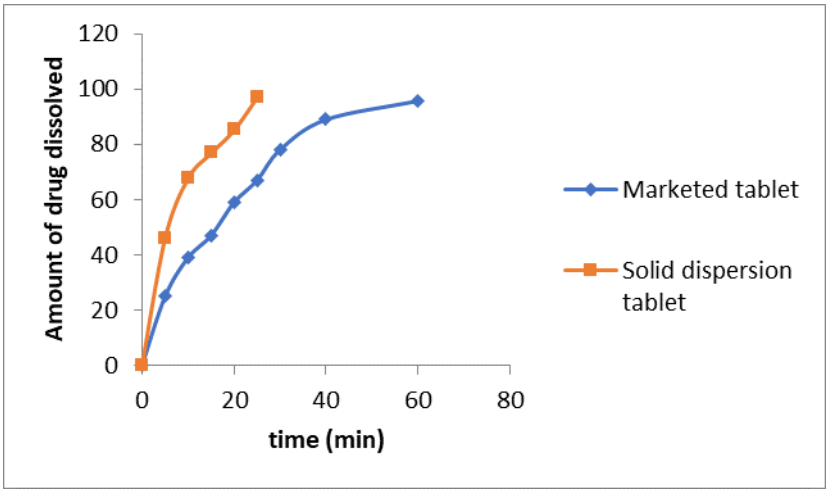

Fig-10: Release order of dissolution profiles

The prepared tablets of Deferasirox showed more in vitro drug release compared to the marketed tablet as shown in table.

Stability study

Drug content before and after stability

Table-9: Drug content before and after stability

% Drug content at 0 month	% Drug content at 1 month
98.56±0.75	98.24±0.86

Drug release profile before and after stability.

Table-10: Drug release profile before and after stability

Time (min)	% drug release at 0 month	% drug release at 1 month
5	0	0
10	44.44±0.62	46.1±0.34
15	64.45±0.67	67.8±0.12
20	75.74±0.72	76.9±0.43
25	82.24±0.79	85.3±0.26
30	*96.64±0.87*	97.2±0.35

The results obtained in the stability test showed that the release rate of Deferasirox tablet stored at a temperature of 40°C and a relative humidity of 75% was unchanged during 1 months of accelerating condition storage.

IV. CONCLUSION

The medicine of choice, Deferasirox, is not very soluble in water. The solid dispersion method involves making them more water-soluble. It was shown that the solid dispersion generated using the solvent evaporation had the largest improvement in solubility and in vitro drug release Its tablets were made. Optimised solid dispersion tablets had better solubility and in vitro drug release than the commercially available version. The chemical composition remained unchanged, according to the FTIR spectra. The DSC verifies the production of solid dispersions. A reduction in crystallinity was seen by X-ray diffraction of the adjusted solid dispersion. The X-ray diffraction analysis of the stabilized optimized solid dispersion revealed no discernible shift in crystallinity, remaining unchanged from before stability. This conclusion that a combination of Deferasirox, Polymer PEG 6000, and poloxamer 188 in a solid dispersion system could improve solubility and dissolution.

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