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Research Article

Formulation and Evaluation of Deferasirox Dispersible Tablets

ARTI MOHAN [1]*, PAYALKESHARVANI[1]

[1]Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bengaluru, Karnataka 560035, India

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ABSTRACT

Deferasirox is an iron chelating agent used for the treatment of chronic iron overload in patients. The objective of present study is to design Deferasirox dispersible tablets to deliver optimum concentration of drug at the desired site, comparable to the innovator product. Various formulations of drug with excipients were evaluated for compatibility and formulations prepared using either the direct compression or wet granulation method and evaluated for pre and post compression parameters and the dissolution data, subjected to kinetic evaluation and compared with that of the innovator product. The drug and the excipients were found to be compatible. Formulation 8prepared by using wet granulation method exhibited disintegration time of (35 sec), dispersion time (67 sec) and percentage of drug release (98.3 %) was found to be satisfactory. So, the batch size was increased in order to check for the reproducibility of the formulation. Optimized formulation followed 1st order kinetics.

INTRODUCTION

In humans total body iron concentration is maintained within the range of 200-1500 mg by adequate adjustment of intestinal absorption, since no excretory mechanism exists. In normal individuals, feedback mechanisms inhibit iron absorption as storage of iron increases. Each condition that induces an increased net entry of iron within the body inevitably leads to iron overload. It can be classified as primary or secondary depending on whether it results from a primary defect in the regulation of iron balance or is secondary to other genetic or acquired disorders. Once iron exceeds a certain level [1], these effects lead to significant morbidity and mortality. The aim of treatment of iron storage, is to remove from the body the excess iron, that has accumulated. This can be done by employing iron chelators. Chelators [2] are small molecules that bind very tightly to metal ions. Some chelators are the molecules that can be easily manufactured (e.g. ethylene di amine tetra acetic acid [EDTA]). The other chelators are complex proteins made by living organisms (e.g. transferrin). The key property shared by all chelators is that the metal ion bound to the chelator is chemically inert.

Author for Correspondence:
Email: artimohan89@gmail.com

Consequently, one of the important roles of chelators is to detoxify metal ions and prevent poisoning. Deferasirox is a chelating agent [3] used for the treatment of chronic iron over loading patients who receive long-term blood transfusions for conditions such as beta-thalassemia and other chronic anemias. It is an iron chelator. The objective of present study is to design and develop Deferasirox dispersible tablets [4] to deliver with optimum concentration of drug at desired site at specific time comparable to the innovator product with better stability, high production feasibility, and excellent patient compatibility [5, 6].

MATERIAL AND METHODS

Materials: Deferasirox was a gift sample from Natco Pharma Limited, Hyderabad, India. All other chemicals and reagents used were of analytical grade.

Methods: Calibration Curve for Deferasirox

50.0mg of Deferasirox was accurately weighed and taken into a 100 ml volumetric flask, dissolved in 10ml of methanol and volume made up with pH 6.8 phosphate buffer+0.5% tween 20 (concentration 500µg/ml). 4ml of stock solution was taken in 100ml volumetric flask and made up with pH 6.8 phosphate buffer+0.5% tween 20 (concentration 20µg/ml). The standard solution

is diluted with dissolution media for obtaining the respective concentrations.

Innovator Product Characterization

Innovator product details including physical parameters and dissolution profile are given in the Table 1 and 2.

Table 1: Physical Parameters of Innovator Product

Dose	400 mg
Weight of the tablet (mg)	1392
Thickness (mm)	5.31
Hardness (kp)	7.2
Length (mm)	17.9
Diagnol (mm)	20.95
Disintegration time (sec)	33
Dispersion time (sec)	60

Table 2: Dissolution Profile of Innovator Product

Time (mins)	Cumulative Percentage Drug release
10	79.7
20	86.4
30	92.1
45	98.6

Pre-Formulation Studies

Drug-Excipient Compatibility Studies

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe.

Compatibility studies were carried out by mixing definite proportions of drug and excipient and kept in glass vials, which are stored at 55°C (2 weeks) and 40±2°C/75±5 % RH(4 weeks).

Pre-Compression Parameters

The formulation blends were evaluated for various pre compression parameters like Angle of Repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio.

Formulation Development of Deferasirox Dispersible Tablets

Procedure for Formulation1

Direct Compression Method: All the ingredients except aerosil and magnesium stearate were weighed and passed through # 40 mesh and mixed for 2 m in a blender, pre-lubricated with aerosil for 5 mins and then lubricated with magnesium stearate in blender for 2 m. The lubricated blend was compressed using 15 mm round flat punches.

Table 3: Formula for F-1

Ingredient	F-1
Deferasirox	400
Lactose monohydrate	144
Crospovidone XL	50
Microcrystalline Cellulose PH102	300
Starch 1500	30
Sodium Lauryl Sulphate	6
Aerosil	10
Magnesium stearate	10
Total	950

Procedure for Formulation 2, 3 and 4

Wet granulation method 1: The Active Pharmaceutical Ingredient, lactose monohydrate, sodium lauryl sulphate, crospovidone XL and micro crystalline cellulose pH 101 were weighed and mixed for 2 m and passed through a # 40 mesh. The binder solution was prepared by dispersing Povidone K30 in sufficient quantity of purified water by stirring. The above mixture was granulated using binder solution and the wet mass was passed through #12 mesh, dried using Fluidized Bed Dryer at 60°C, until the moisture content in the blend was 1.0 to 2.0%.The dried blend was then passed through #18 mesh and pre-lubricated with aerosil for 5 m and then lubricated with magnesium stearate in blender for 2 m. Finally the lubricated blend was compressed using 15 mm round flat punches.

Procedure for Formulation 6

Wet granulation method 2: All the above ingredients for formulation 2, 3 and 4 along with starch 1500 were weighed and mixed for 2 m and passed through #40 mesh. The binder solution was prepared by dispersing Povidone K30 in sufficient quantity of water by stirring. Sodium Lauryl Sulphate was added to the binder solution and allowed to dissolve and added to the dry mixture. The wet mass was passed through #12 mesh. The sieved mixture was dried using Fluidized Bed Dryer at 60°C until the moisture content in the blend became to 1.0 to 2.0% and passed through #18 mesh. The sieved mixture was lubricated with aerosil, crospovidone XL and sodium lauryl sulphate for 2 m. Magnesium stearate was passed through

#40 mesh and added to the above mixture and then mixed for 2 m. Then finally the lubricated blend was compressed using 15 mm round flat punches.

Procedure for Formulation 7: All ingredients in Formulation 6 except lactose monohydrate were weighed and mixed for 2 m and the same procedure followed as for Formulation 6.

Procedure for Formulation 8: All ingredients in Formulation 7 along with sucralose were weighed and mixed for 2 m and the same procedure followed as for Formulation 6.

Procedure for Formulation 9: Active Pharmaceutical Ingredient, cross-povidone XL, micro crystalline cellulose pH 101, starch 1500, sucralose were weighed and mixed in Rapid Mixer Grinder for 5 m. The impeller was adjusted slow. The binder solution was prepared by dispersing Povidone K30, SLS and colour slowly in sufficient quantity of water by stirring. The binder solution was added to the dry mixture within 2 m with impeller adjusted fast. The wet mass was mixed for 1 m with impeller. The wet mass was dried using Fluid Bed Dryer at 60°C until the moisture content became 1.0 to 2.0%, passed through #18 mesh and lubricated with sodium lauryl sulphate, aerosil, cross-povidone XL, flavour and magnesium stearate in a blender. Then finally the lubricated blend was compressed using 15 mm round flat punches.

Table 4: Formula for F-2, F-3, F-4, F-6, F-7, F-8, F-9

Ingredient	F-2	F-3	F-4	F-6	F-7	F-8	F-9
Deferasirox	400	400	400	400	400	400	400
Lactose monohydrate	97	97	97	97	-	-	-
Crospovidone XL	25	30	35	50	100	100	100
Microcrystalline CellulosePH101	333.5	308.5	303.5	258.5	305.5	292	292
Starch 1500	-	-	-	30	30	30	30
Povidone K30	25	45	45	45	45	45	45
SLS	6	6	6	6	6	6	6
Sucralose	-	-	-	-	-	8	8
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Color	-	-	-	-	-	0.5	0.5
Aerosil	9	9	9	9	9	9	9
Flavour	-	-	-	-	-	5	5
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Total	900	900	900	900	900	900	900

Procedure for Formulation 5:

Wet granulation method 2: Active Pharmaceutical Ingredient, sodium starch glycolate, micro crystalline cellulose PH101, hydroxy propyl cellulose (L-HPC-LH11) were weighed and mixed for 2 m and passed through #40 mesh.The binder solution was prepared by dispersing Povidone K30 and Tween 80 in sufficient quantity of water and added to the dry mixture until a wet mass is formed, passed through #12 mesh.and dried using Fluidized Bed Dryer at 60°C until the moisture content in the blend becomes 1.0 to 2.0%.The dried mixture was passed through #18 mesh, lubricated with sodium starch glycolate, aerosil and talc first for 2 m and then mixed with sodium starch fumarate for 1-2 m.Then the lubricated blend was passed through #40 mesh and compressed using 15 mm round flat punches.

Table 5: Formula for F-5

S.No	Ingredient	mg/tab (F-5)
1	Deferasirox	400
2	SSG	80
3	MCC PH 101	302
4	L-HPC-LH11	44
5	Tween 80	4
6	Povidone K30	45
7	Water	q.s
8	Aerosil	10
9	SSF	6
10	Talc	9
	Total	900

Post-Compression Parameters [7]: Formulated dispersible tablets were evaluated for their Physical appearance, Weight variation, Hardness, Thickness, Percentage Friability, Disintegration time and Uniformity of dispersion.

Assay for Percentage of Drug Content [8]: 20 tablets were accurately weighed and powdered and tablet weight equivalent to 400 mg of Deferasirox was weighed and transferred into a 250 ml volumetric flask. To this 180 ml of the diluent was added and sonicated for 30 m with occasional stirring. Then the solution was cooled to room temperature and diluted to the required volume with diluent. The solution was filtered through 0.45µm membrane filter, 1.0 ml of the above filtered solution was transferred into a 200 ml volumetric flask and diluted to the required volume with diluent.

Procedure

Equal volumes (10 µl) of the diluent as blank, standard preparation and sample preparations were injected separately into the chromatograph, the chromatograms were recorded and the peak area responses for the major peaks were measured. Finally the percentage content of Deferasirox in the portion of the Deferasirox tablets was calculated.

$$\%\ Content\ of\ Deferasirox = \frac{TA * SW * 2 * 250 * 200 * P * Avg.wt * 100}{SA * 100 * 100 * TW * 1 * 100 * LA}$$

Where,

TA = Peak area response due to Deferasirox from sample preparation.

SA = Peak area response due to Deferasirox from standard preparation.

SW = Weight of Deferasirox working standard taken in mg.

TW = Weight of sample taken in mg.

P = Purity of Deferasirox working standard.

Avg. wt = Average weight of Deferasirox tablet taken in mg.

LA = Labeled amount of Deferasirox.

Dissolution Studies [9]: The *In vitro* dissolution study was carried out in the USP dissolution test apparatus, type II (paddle). One tablet was placed in each of the six dissolution flasks containing 900ml of dissolution medium, previously maintained at 37°C ± 0.5°C.

After completion of each specified time interval, a portion of the solution was withdrawn from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1 cm from vessel wall and filtered through 0.45 µm membrane filter. The samples were collected at specified time intervals and diluted to required volume with dissolution medium.

The absorbance of the standard and sample preparations was measured in 1 cm cells, with a suitable spectrophotometer using dissolution medium as blank. Finally the % drug dissolved of Deferasirox tablets was calculated.

Stability Studies [10]: The final formulation was packed in suitable packing like blister packs and HDPE bottles and kept at different temperature, humidity conditions and samples analyzed for physical and chemical properties and dissolution for 2 months.

In-Vitro Dissolution Kinetic Studies [11]: *In-vitro* release data was plotted and tested with zero-order (cumulative % drug release versus time) and first order (log% drug remained vs. time) models and the regression analysis with correlation coefficient R^2 value for different kinetic models which is an indicative of the linearity of plot was summarized in a table.

RESULTS AND DISCUSSION

Deferasirox is indicated in for the treatment of Chronic Iron Overload [12] due to blood transfusions in adult and paediatric patients (aged 2 years and over).

Calibration Curve for Deferasirox

Calibration Curve for Deferasirox in pH 6.8 phosphate buffer indicated good linearity with r^2value of 0.9991 and y=0.0627x which suggests that it obeys the "Beer–Lambert" law.

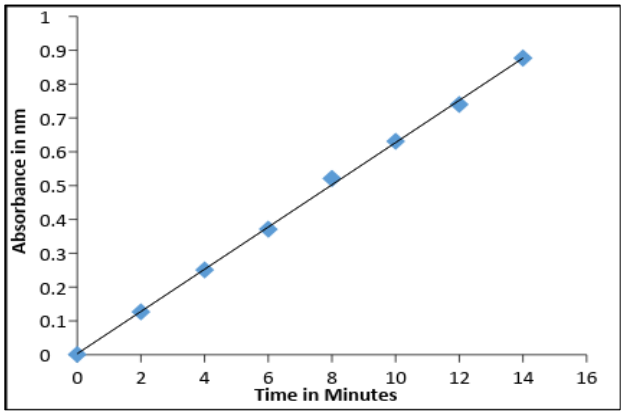

Figure 1: Calibration Curve for Deferasirox in pH 6.8 Buffer

Table 6: Drug-Excipient Compatibility Studies

S.No	Ingredients	Ratio	Description		
			Initial	55°C (2 weeks)	40±2°C /75±5 % RH (4 weeks)
1	API	1	Off white	No change	No change
2	Lactose monohydrate	1	Off white	No change	No change
3	Crospovidone XL	1	White	No change	No change
4	Starch 1500	1	White	No change	No change
5	MCC PH 101	1	Off white	No change	No change
6	SLS	1	White	No change	No change
7	Povidone K30	1	Off white	No change	No change
8	Aerosil	1	White	No change	No change
9	Magnesium stearate	1	White	No change	No change
10	L-HPC-LH11	1	White	No change	No change
11	SSG	1	White	No change	No change
12	Tween 80	1	Pale yellow	No change	No change
13	SSF	1	White	No change	No change
14	Talc	1	White	No change	No change
15	Sucralose	1	White	No change	No change
16	Orange flavor	1	Off white	No change	No change
17	Sunset yellow(SUPRA)	1	Reddish yellow	No change	No change
18	API+ Crospovidone XL	5:1	Off white	No change	No change
19	API+ Starch 1500	5:1	Off white	No change	No change
20	API+ MCC PH 101	1:5	Off white	No change	No change
21	API+ SLS	5:1	Off white	No change	No change
22	API+ PovidoneK30	5:1	Off white	No change	No change
23	API+ Aerosil	5:1	Off white	No change	No change
24	API+ Magnesium stearate	5:1	Off white	No change	No change
25	API+L-HPC-LH11	5:1	Off white	No change	No change
26	API+SSG	5:1	Off white	No change	No change
27	API+Tween 80	5:1	Pale yellow	No change	No change
28	API+SSF	5:1	Off white	No change	No change
29	API+Talc	5:1	Off white	No change	No change
30	API+ Sucralose	5:1	Off white	No change	No change
31	API+ Orange flavor	5:1	Off white	No change	No change
32	API+ Sunset yellow(SUPRA)	5:1	Pale pink	No change	No change

Table 7: Pre-Compression Parameters for Formulations F-1 TO F-9

Formula	Angle of repose	Compressibility Index (%)	Hausner's ratio	Loss On Drying (%)
F-1	45.80	26.40	1.36	2.37
F-2	30.32	25.26	1.33	1.93
F-3	25.70	24.74	1.32	2.01
F-4	28.28	23.20	1.30	1.59
F-5	32.16	18.23	1.25	1.87
F-6	30.34	17.50	1.21	1.41
F-7	26.59	13.00	1.15	1.32
F-8	**25.26**	**12.26**	**1.14**	**1.28**
F-9	25.12	12.44	1.13	1.27

Pre-Formulation Studies

Drug-Excipient Compatibility Studies

Pre-formulation studies were performed for the drug and excipients as per the standard procedures.

Drug-excipient compatibility studies indicated compatibility between the drug and the excipient as shown in Table 4.

Pre-Compression Parameters

Pre-compression parameters for formulations F1 to F9 such as Angle of Repose, Compressibility Index, Hausner's Ratio and Loss on Drying were found to be within acceptable range as seen in Table 5.

Post Compression Parameters: Post compression parameters for formulations F-1 to F-9.

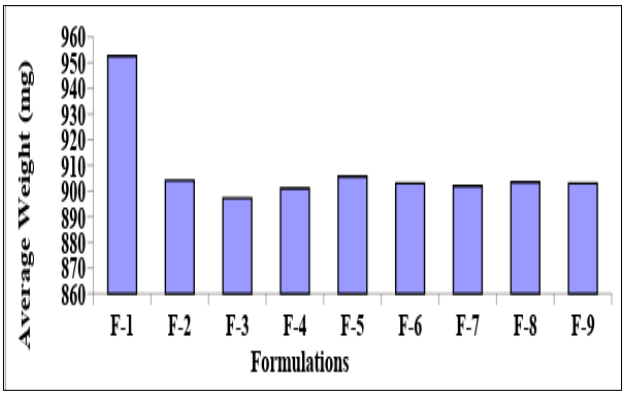

Figure 2: Comparison of Average Weight of Different Formulations

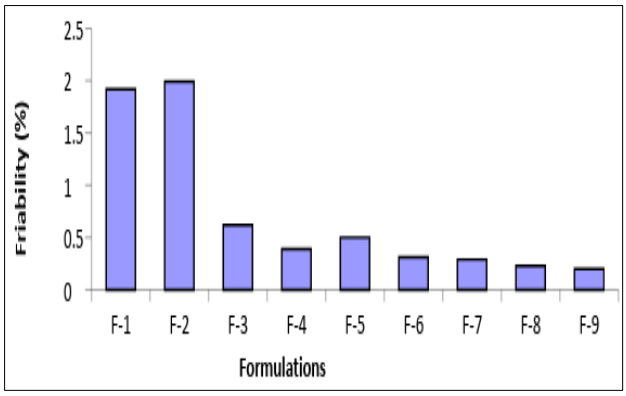

Figure 5: Comparison of Percentage Friability of Different Formulations

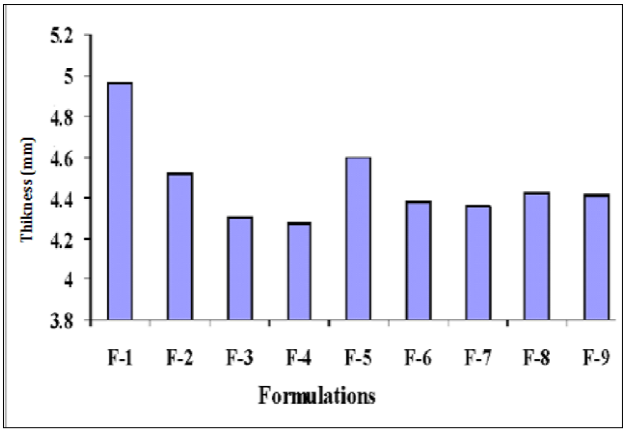

Figure 3: Comparison of Thickness of Different Formulations

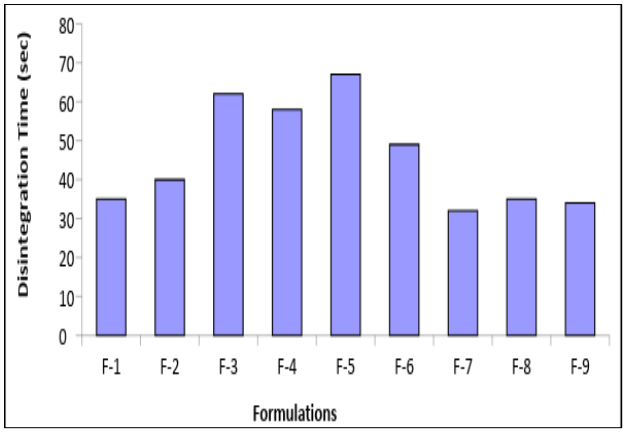

Figure 6: Comparison of Disintegration Time of Different Formulations

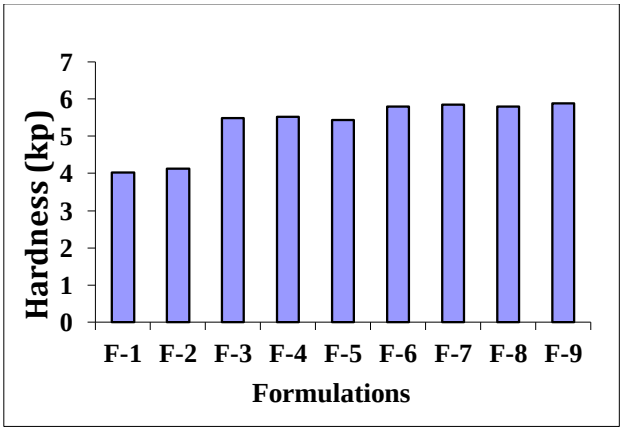

Figure 4: Comparison of Hardness Of Different Formulations

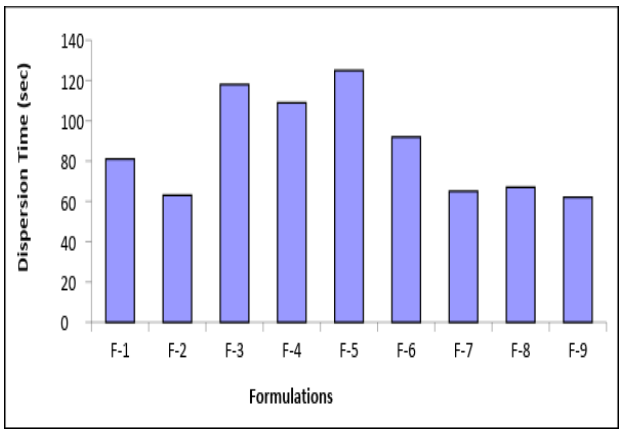

Figure 7: Comparison of Dispersion Time of Different Formulations

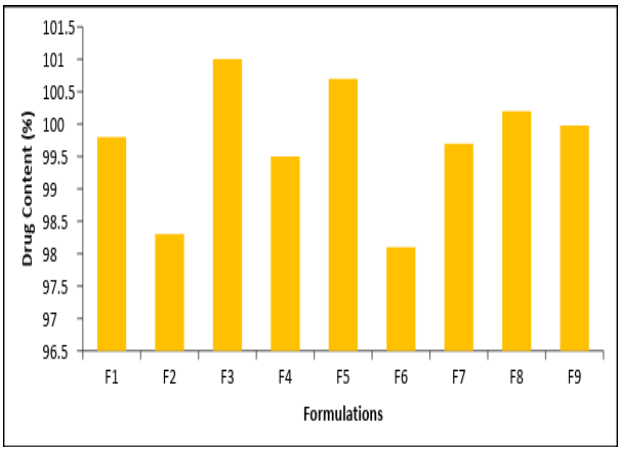

Figure 8: Comparison of Percentage of Drug Content of Different Formulations

Post compression parameters for formulations are shown in Figures 2 to 8.

Formulation 1 was made by direct compression method and exhibited poor flow property, hardness and friability.

Formulations 2,3,4,6,7,8,9 were made by using wet granulation method. In formulation-2 hardness was found to be less and the friability value did not comply with the specifications. In formulations 3, 4 and 6, the concentration of super disintegrant was increased in order to get a better dispersion. Here the disintegration time, dispersion time and percentage of drug release did not comply with the innovator product. In formulations 7, 8, 9 the disintegration time, dispersion time and percentage of drug release were found to match with the innovator product. All the physicochemical characteristics of the finished product were found to be satisfactory.

Formulation 5 was also made by wet granulation method but with a different formula. Here the disintegration time, dispersion time and percentage drug release does not match with the innovator [13].

Dissolution Studies

Table 8: Dissolution Profiles of Different Formulations (F-1 to F-9)

Sampling Time (minutes)	Cumulative Percentage Drug Release								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	F-9
10	72.5	50.7	49.6	54.9	56.8	69.6	78.4	77.2	**78.0**
20	78.0	66.4	63.3	70.0	60.2	80.5	84.3	84.8	**85.1**
30	83.6	78.5	74.1	79.5	65.3	87.7	90.1	91.4	**90.6**
45	**88.8**	**87.9**	**86.4**	**89.3**	**73.6**	**91.4**	**97.2**	**98.3**	**97.4**

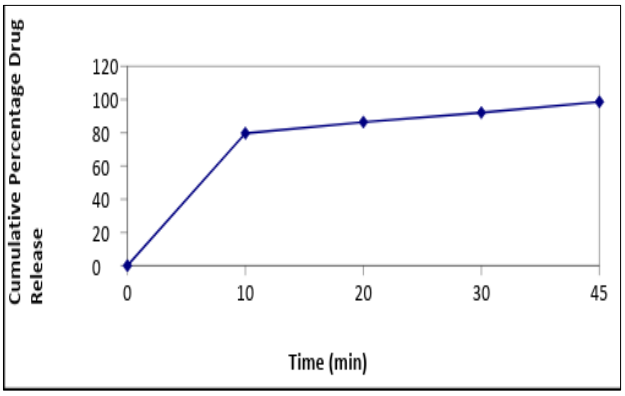

Figure 9: Dissolution Profile of Deferasirox Innovator

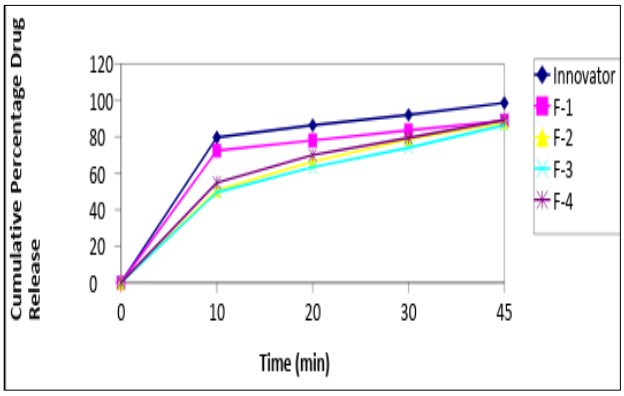

Figure 10: Dissolution Profile of Formulations 1-4 Compared With the Innovator

Here in an attempt is being made to improvise each subsequent formulation depending upon the drug release profile of the previous formulation. The percentage of drug release was 88.8% for F1 which does not comply with the innovator product. So the next batch F2 was formulated using wet granulation method. F2 exhibited 87.9 percent of drug release which was less as compared to the innovator and hence F3 was formulated by increasing both the binder and super disintegrant concentrations. For F3 the percentage of drug release was found to be 86.4% and therefore super disintegrant concentration was increased for F4 which showed drug release of 89.3 %.

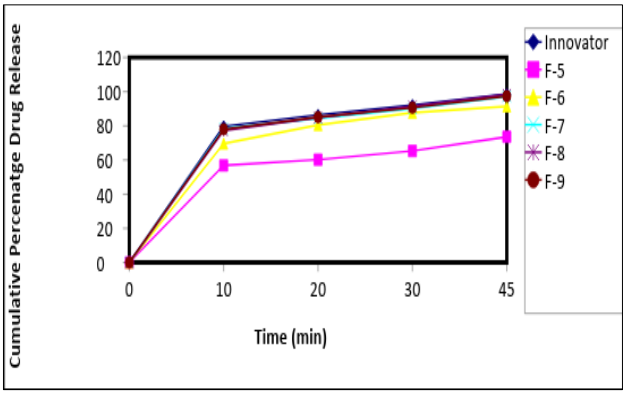

Figure 11: Dissolution Profile of Formulations 5-9 Compared With the Innovator

Formulation F-5 was made by using a new formula. The percentage of drug release was 76.3 % for F5 which does not comply with the innovator product. In order to get a better dispersion the next batch F6 was planned by incorporating starch 1500to F4 formulation and increasing the concentration of super disintegrant. F6 exhibited 91.4 percent of drug release which again does not comply with the innovator product. Formulation F-7 was made by using the same formula as of the previous batch by excluding lactose monohydrate and the concentration of super disintegrant was increased to 100mg/tab. The disintegration time (32 sec) and the dispersion time (65sec) were found to be satisfactory and the percentage of drug release (97.2 %) also improved as compared to the previous batches and it was found to match with the innovator product. Hence, the next batch F8 was formulated by adding colour, flavour and sweetener for better taste and appearance of the tablet. For F8 the disintegration time (35 sec), dispersion time (67 sec) and the percentage of drug release (98.3 % in 45 mins) were found to be satisfactory and matching with the innovator product and F9 was formulated by increasing the batch size to check for the reproducibility of the formula.

Stability Studies

Table 9: Physical and Chemical Parameters of Deferasirox Dispersible Tablets (F-8) After 1st And 2nd Month at 40±2°C/75±5 % RH (Packing: HDPE Bottle)

Parameter	Initial	1 Month	2 Month
Description	Light orange coloured round shaped uncoated tablets	No change	No change
Avg.wt (mg)	903.0	903.2	903.4
Hardness (kp)	5.89	5.83	5.77
Thickness (mm)	4.41	4.48	4.53
Friability (%)	0.20	0.23	0.26
Water content (w/w)	3.7	3.8	3.5
Assay (%)	99.98	100.5	99.47

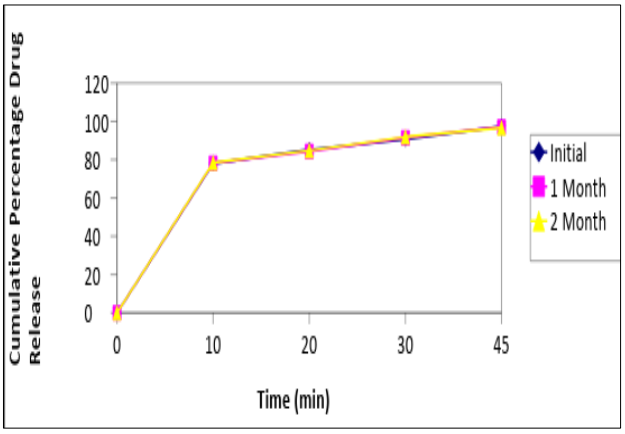

Figure 12: Graphical Representation of Dissolution Profiles of Stability Studies Conducted at 40±5°C/75±5 % RH for Formulation 8 (Packing: HDPE Bottle)

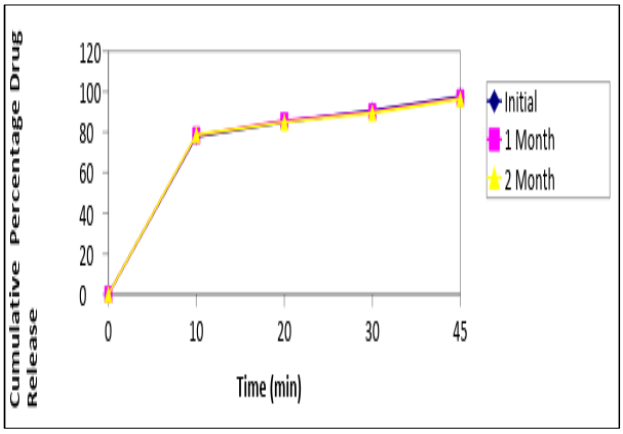

Figure 13: Graphical Representation Of Dissolution Profiles Of Stability Studies Conducted At 40±2°C/75±5 % Rh For Formulation 8 (Packing: Blister Pack)

Table 10: Physical and Chemical Parameters of Deferasirox Dispersible Tablets (F-8) After 1st And 2nd Month at 40±2°C/75±5 % Rh (Packing: Blister Pack)

Parameter	Initial	1 Month	2 Month
Description	Light orange coloured round shaped uncoated tablets	No change	No change
Avg.wt (mg)	903.0	903.2	903.1
Hardness (kp)	5.89	5.86	5.82
Thickness (mm)	4.40	4.50	4.54
Friability (%)	0.20	0.24	0.23
Water content (w/w)	3.7	3.6	3.8
Assay (%)	99.98	100.2	99.41

Physical and chemical parameters and dissolution profiles of Deferasirox dispersible tablets (F-8) after 1st and 2nd month at 40±2°C /75±5 %RH were found to be stable after being packed in both, HDPE bottle and blister packs.

In-Vitro Dissolution Kinetic Studies

Table 11: Release Kinetics of the Optimized Formulation

Release kinetics	Correlation coefficient
Zero-order	0.646
First order	0.964

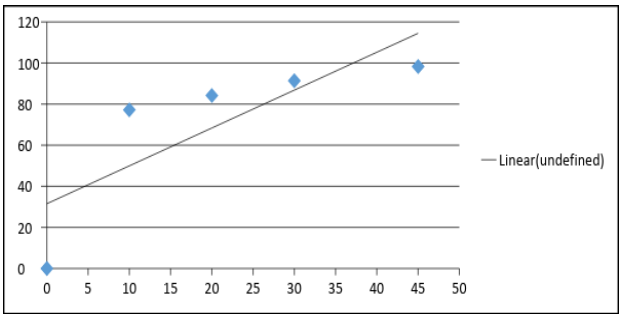

Figure 14: Zero-Order Release Kinetics

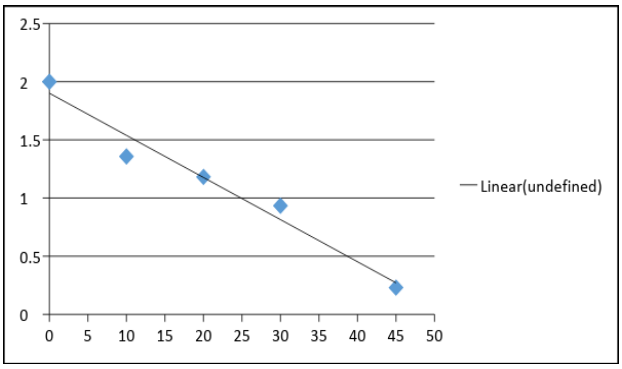

Figure 15: First Order Release Kinetics

Zero and first order kinetic models were applied to the optimized formulation and observed that the formulation followed 1st order kinetics which was confirmed by higher correlation coefficient values for the same and also complies with the innovator product.

CONCLUSION

All the formulations were subjected to physicochemical analysis and out of them *Formulation 8* was found to be satisfactory as compared to other formulations. The disintegration time (35s), dispersion time (67s) and percentage of drug release (98.3 %) were found to be satisfactory and matches with the innovator. So, the batch size was increased in further trial to check the reproducibility (*Formulation 9*).

Table 12: Formula for Finalized Formulation (F-9)

S.No	Ingredient	mg/tab (F-8)
1	Deferasirox	400
2	Crospovidone XL	100
3	Micrcrystalline cellulose PH101	292
4	Starch 1500	30
5	Povidone K30	45
6	Sodium Lauryl Sulfate	6
7	Sucralose	8
8	Water	q.s
9	Colour	0.5
10	Aerosil	9
11	Flavour	5
12	Magnesium stearate	4.5
	Total	**900**

Thus it was concluded that it is possible to formulate Deferasirox Dispersible Tablets by using the above mentioned method.

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