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RESEARCH ARTICLE

FORMULATION AND IN VITRO EVALUATION OF DEFERASIROX ORO-DISPERSIBLE TABLETS

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Abstract:
Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in technology, led to the development of oro-dispersible tablets (ODT's) with improved patient compliance and convenience. Deferasirox an oral iron chelator is used in patients suffering from chronic iron over load and treatment of patients with anemia. Deferasirox is a poorly soluble drug so; ODT's is prepared to increase the release rate. The present work is carried out by using super disintegrants such as crospovidine, croscarmellose sodium and sodium starch glycolate (SSG). All these formulations are compressed by direct compression technique. The developed tablets are evaluated for hardness, weight variation, friability, dispersion time, disintegration time and in -vitro dissolution studies. The tablet is compared with an innovator (ASUNRA 400mg, NOVARTIS) and is concluded that dispersible tablets of Deferasirox (400mg) with the superdisintegrant crospovidone (total weight of tablet-900 mg) showed rapid release rate and enhance dissolution. The developed Deferasirox ODT's has better patient compliance and effective therapy.

Keywords: oro-dispersible tablets, Deferasirox, croscarmellose sodium, ASUNRA

Introduction

Dispersible tablets as defined in European pharmacopoeia are uncoated or film coated tablets intended to be dispersed in water before administration giving a homogenous dispersion. Typically, a dispersible tablet is dispersed in about 5-15ml of water and the resulting dispersion is administered to the patient. However, they can also be placed directly on the tongue and sucked. Dispersible tablets are required to disintegrate within 3 minutes in water at 15-25 ^{0}C. Also the dispersion produced from a dispersible tablet should pass through a sieve screen with a nominal mesh aperture of 710 microns [1]. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy [2].Orodispersible tablets are gaining prominence as new drug delivery systems.

These dosage forms dissolves or disintegrate in oral cavity within a minute without the need of water or chewing [3]. In this study, an effort has been made to formulate oro dispersible tablets of Deferasirox using different disintegrants. Chelators are small molecules that bind very tightly to metal ions. Some chelators are the molecules that can be easily manufactured (e.g. ethylene diamine 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. Consequently, one of the important roles of chelators is to detoxify metal ions and prevent poisoning. Deferasirox belongs to a new class of oral tridentate chelator, N-substituted bishydroxy Phenyltriazoles [4].

With a plasma half-life of 8 to 16 hours and once-daily dosing permits circulating drug at all times to scavenge the non–transferrin-bound "labile plasma iron" responsible for tissue damage in iron-overloaded subjects, by means of toxic oxygen. Deferasirox-iron complexes are excreted in the stool[5]. 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 anemia [6]. Though the conventional oral tablets are widely used, they suffer from a few practical drawbacks such as its no suitability when quick onset of action is required. Often time people experience inconvenience using conventional oral dosage forms in mentally ill and uncooperative patients. Sometimes it may be difficult to swallow conventional products due to unavailability of water [7, 8.] Hence the present work was aimed to formulate the oro dispersible tablets of Deferasirox using crospovidine, croscarmellose sodium and sodium starch glycolate (SSG) as a disintegrants. Orodispersible tablets are those when put on tongue disintegrate instantaneously, releasing the drug which dissolve or disperses in the saliva [9]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both, industry and academia. Their growing importance was underline recently when European pharmacopoeia adopted the term "Orodispersible Tablet" as tablet that is to be place in the mouth where it disperses rapidly before swallowing[1, 10].

MATERIALS & METHODS

Deferasirox was obtained as gift samples from Natco Pharma Ltd, Hyderabad. Methyl cellulose PH 101, Methyl cellulose PH 102 and Povidone K30 were the gift samples from Signet Chemical Corporation, Mumbai. Crospovidone XL was obtained as gift samples from Ansul Agencies, Mumbai. Starch 1500 and Sodium starch glycolate were obtained as gift samples from KMV Enterprises, Hyderabad All other chemicals and reagents used were either of analytical or pharmaceutical grades.

Pre-formulation studies[11]

Drug-excipient compatibility studies

The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe. The compatibility studies provide the framework for the drugs combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets. 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).

Calibration curve for Deferasirox

A standard graph of pure drug in suitable medium was prepared by plotting the concentration on X-axis and absorbance on Y-axis. An accurately weighed 100 mg of Deferasirox was dissolved in pH 6.8 phosphate buffer as per I.P and make up the volume up to 100 ml in a volumetric flask, (Stock Solution: I, This stock solution concentration is 1mg/ml or 1000 µg/ml). From this stock solution 10 ml of solution were pipette out and make up the volume up to 100 ml (Stock Solution: II, 100µg/ml). Then the aliquots were prepared, whose concentration ranging from 10 to 50 µg/ml and the absorbance were measured at 245 nm by using UV Spectrophotometer Labomed, (Model No: 2602) against the reagent blank. The coefficient of variation and correlation coefficient were determined.

Micromeritic characterization of Precompressed blend [11]

The characteristic parameters of the precompressed blend were evaluated. The angle of repose and flow rate were determined by the funnel method. The bulk density and tapped density were determined by the cylinder method and Carr's index was calculated using the following equation

Carr's index $= Df - D0/Df \times 100$

Where, Df= Poured bulk or bulk density, $D0$ = Tapped or consolidated bulk density.

Loss on drying

The Loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (1g) was determined by using electronic LOD (helium lamp) apparatus at 105°C.

Preparation of Orodispersible tablets

Deferasirox oro dispersible tablets were prepared by direct compression method according to formula given in the (Table 1). A total number of nine formulations were prepared. All the ingredients were passed through 60-mesh sieve separately and collected. The drug and lactose were mixed in small portion of both at each time and blended to get a uniform mixture and kept aside. Then the ingredients were weighed and mixed in geometrical order and the tablets were compressed using

flat face 12 mm size punch to get a tablets of 900 mg weight using single punch tablet compression machine (Cadmach machinery Limited, Ahmadabad)[12].

Evaluation parameters of Dispersible tablets[13]

Physical appearance
The tablets were inspected for smoothness, absence of cracks, chips and other undesirable characteristics. If they are colored, it includes examination for mottling and other evidence of non uniform color distribution except where they are used intentionally.

Weight variation test
20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight and the SD was calculated.

Hardness
The hardness test is performed to measure the tablet strength. Tablet should be hard enough to withstand packing and shipping. Schluenzier hardness tester was used for the determination of hardness of tablets. The hardness of 10 tablets was noted and the average hardness was calculated. It is expressed in KP or kg/cm^2.

Thickness
Thickness was determined for 20 pre weighed tablets of each batch using a digital Vernier scale and the average thickness was determined in mm**.** The thickness of the tablet is mostly related to the tablet hardness and can be used as an initial control parameter.

Percentage Friability
The friability test gives an indication of tablets ability to resist chipping and abrasion on handling during packaging and shipping. Usually for conventional tablets friability value of 1.0% or less is desirable. If the tablet weight is ≥ 650 mg 10 tablets (USP) are taken and initial weight was noted. The tablets were rotated in the Roche friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed.
The tablets that loose less than 1% weight were considered to be compliant.

The percentage friability is expressed as the loss of weight and is calculated by the formula

$$\% \text{ Friability} = (A\text{-}B/B) \times 100$$

Where, A = Initial weight of tablets, B = Final weight of tablets after 100 revolutions

Uniformity of dispersion
This test was applicable only to dispersible tablets. In this method, two tablets were placed in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion must be obtained which passes through a sieve screen with a nominal mesh aperture of 710 µm (sieve no. 22).

Disintegration time
Disintegration time is the time required for a tablet to break up into granules of specified size (or smaller), under carefully specified test conditions. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm length and 2.15 mm in diameter the bottom of which consists of a 10 mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900 ml which is maintained at 37±2°C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet. This test is performed to ensure disintegration of tablets in water, if it is to be used as a dispersible tablet. Dispersible tablets must disintegrate within 3 mins when examined by the disintegration test for tablets as per the compliance in the pharmacopoeia.

Dissolution study (By UV method)
The dissolution test measures the rate of release of the drug from the dosage form *in vitro*, it is usually expressed as extent of dissolution (% drug content) occurring after a given time under specified conditions.

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 900 ml of dissolution medium, (pH 6.8 phosphate buffer containing 0.5% tween -20) previously maintained at 37°C ± 0.5°C. After completion of each specified time interval, 2ml 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 (10.20, 30, 45min) 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 preparation. Finally the % drug dissolved of Deferasirox tablets was calculated.

Assay (By HPLC method)

Instrument: High performance liquid chromatography equipped with UV Detector and data handling system

Chemicals and reagents

- Ammonium dihydrogen orthophosphate
- Ortho-phosphoric acid
- Purified water
- Acetonitrile- HPLC grade
- Methanol- HPLC grade
- Deferasirox working standard
-

Chromatographic conditions

Column : Develosil ODS HG-5 (150×4.6mm) 5µm

Flow rate : 1.5 ml/min
Injection volume : 10 µl
Column temperature: 40°C
Runtime : 15 min

Preparations:

Mobile phase preparation
1.58 g of Ammonium dihydrogen orthophosphate was accurately weighed into a 1000ml beaker. To that 550 ml of purified water was added and mixed. The pH of the solution was adjusted to 2.5 using ortho-phosphoric acid. This solution and acetonitrile were mixed in the ratio of 550:450 respectively. Finally the solution was filtered using 0.45 µm membrane filter paper and degas.

Diluent preparation
Acetonitrile and methanol were mixed in the ratio of 50:50 v/v respectively.

Standard preparation
40 mg of Deferasirox working standard was accurately weighed and transferred into a 100 ml volumetric flask. Then 60 ml of diluent was added and was dissolved by sonication. The solution was cooled to the room temperature and diluted to the required volume with diluent.
2 ml of the above solution was transferred into a 100 ml volumetric flask and diluted to the required volume with diluents (acetonitrile: methanol).

Sample preparation
20 tablets were accurately weighed and finally powdered. From this powdered tablet equivalent to 400 mg of Deferasirox was weighed and transferred into a 250 ml volumetric flask, to this 180 ml of the diluent (acetonitrile: methanol) was added and sonicated for 30mins with occasional stirring. Then the solution was cooled to room temperature and diluted to the required volume with diluent. The solution was filtered through 0.45 µm membrane filter. 1.0ml 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 (acetonitrile: methanol) 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.

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

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 = Label amount of Deferasirox.

Water content (By KF Method)

Instrument: Karl Fischer Titrator
35 ml of a mixture of methanol was transferred to the titration vessel and titrated with Karl Fischer reagent to the electrometric end point, to consume any moisture that may be present (disregard the volume consumed, since it does not enter into the calculation).
5 tablets was ground to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results. 300-500 mg of the powder was accurately weighed and transferred into the titration vessel, mixed and titrated with Karl Fischer reagent to the electrometric end point. Finally the water content of the specimen in mg was calculated.

Stability studies[14]
The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc).

The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples were withdrawn after 1st month and 2nd month and evaluated for change in *invitro* drug release and physical appearance.

RESULTS & DISCUSSION

Drug –Polymer compatibility studies by FT-IR

The FT-IR spectra of the physical mixture were compared with the FT-IR spectra of the pure drug. (Figure 1) The results indicated that the characteristic absorption peaks due to pure Deferasirox have appeared in the formulations, without any significant change in their position, indicating no chemical interaction between Deferasirox and Polymers

Calibration curve for Deferasirox

The prepared aliquots, whose concentration ranging from 10 to 50 µg/ml absorbance was measured at 245 nm by using UV Spectrophotometer against the reagent blank. A standard graph of pure drug in suitable medium was prepared by plotting the concentration (µg/ml) on X-axis and absorbance (nm) on Y-axis (Figure 2). An excellent correlation co-efficient (r^2=0.999) was observed.

Micromeritic characterization of precompressed powder blend

The Micromeritic property of powder blend of all formulations were characterized with respect to the angle of repose, bulk density, tap density, hausner's ratio and Carr's index (Table 2).the Micromeritic property of all formulations were comply with pharmacopoeial specifications.

Physical Evaluation of tablets

The formulated tablets were subjected for various evaluation parameters like hardness, thickness, weight variation, friability and LOD test. Our experimental results (Table 3) revealed that all the formulated tablets were of good quality with regard to hardness (4- 6 kg/cm2), friability (below 1% except batch F-1) and thickness (4.25 to 4.90 mm). The weight variation of the tablet (below 5%) complying with pharmacopoeial specification. The LOD was found to be within the limits (Below 2%) which show that the drug was uniformly distributed in all the formulations.

The formulated tablets were subjected for various evaluation parameters like Disintegration time, Dispersion time, Water content and assay. Our experimental results (Table 4) revealed that all the formulated tablets were of good quality with regard to Disintegration time (33-67 sec), Dispersion time (63-123 sec) and assay (more than 85 %).

Dissolution study (By UV method)

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. Dissolution was taken according to lotter et.al using paddle type-II apparatus of USP, (**DBK instruments, Mumbai**) in 6.8 pH phosphate buffer (900ml) medium, at 75 rpm, and at 37±0.5ºc. 900mg of Deferasirox tablet was placed in dissolution media and 5ml of sample was withdrawn at time(min) 5,10,15,20,25,30 respectively and diluted up to 50ml (DF=10) and then analyzed with double beam spectro photometer (figure 4). The dissolution was carried out for different experimental trials and also for the innovator product. Formulation 2 and 3 were showing very less drug release after 40 min. Even though other formulation trails were having less drug release after 40 min, due to the processing problems encountered in the manufacture of tablets, they were not considered to be successful. F8 was showing good drug release profile, without any processing problems, from the results it was concluded that the formulation F8 was showing good *In Vitro* dissolution profile and similar to that of innovator's dissolution profile

Stability studies

Stability studies of the formulation F8 of Deferasirox oro dispersible tablets were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 40 ºC/75% RH for 30 and 60 days. There was no significant change in the physical property and drug content during the study period. (Table 6 and figure 5)

CONCLUSION

Deferasirox is indicated in for the treatment of Chronic Iron Overload due to blood transfusions in adult and pediatric patients (aged 2 years and over). Pre-formulation studies were performed for the drug and excipients as per the standard procedures. The innovator product characterization was performed. Formulation 1 was made by direct compression method. In this poor flow property was observed and also hardness and friability values were not satisfactory. Formulations 2,3,4,6,7,8,9 were made by using direct compression method. In formulation 2 hardness was found to be less and the friability value does not comply with the specifications. In formulations 3, 4, 6 in order to get a better dispersion the concentration of Superdisintegrant was increased. Here the disintegration time, dispersion time and percentage of drug release does 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. Formula 5 was also made by direct compression method but with a different formula. Here the disintegration time, dispersion time and percentage drug release does not match with the innovator. All the formulations were subjected to physicochemical analysis and out of them. Formulation 8 was found to be satisfactory when

Table 1: Preparation of Orodispersible tablets

S.No	Ingredient	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1	Deferasirox	400	400	400	400	400	400	400	400	400
2	Lactose monohydrate	144	97	97	97	-	97	-	-	-
3	Crospovidone XL	50	25	30	35	-	50	100	100	100
4	MCC PH 101	-	333.5	308.5	302.5	302	258.5	305.5	292	292
5	MCC PH 102	300	-	-	-	-	-	-	-	-
6	Starch 1500	30	-	-	-	-	30	30	30	30
7	Povidone K30	-	25	45	45	45	45	45	45	45
8	SLS	6	6	6	6	-	6	6	6	6
9	SSG	-	-	-	-	80	-	-	-	-
10	Sucralose		-	-	-	-	-	-	8	8
11	L-HPC-LH11	-	-	-	-	44	-	-	-	-
12	Tween 80	-	-	-	-	4	-	-	-	-
13	Talc	-	-	-	-	9	-	-	-	-
14	Aerosil	10	9	9	9	10	9	9	9	9
15	Magnesium stearate	10	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
16	Color	-	-	-	-	-	-	-	0.5	0.5
Total weight		950	900	900	900	900	900	900	900	900

Figure 1.1: FT-IR of Deferasirox

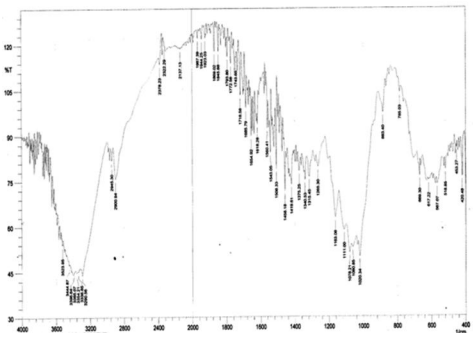


Figure 1.2: FT-IR of Deferasirox+SSG+MCC+ PVP

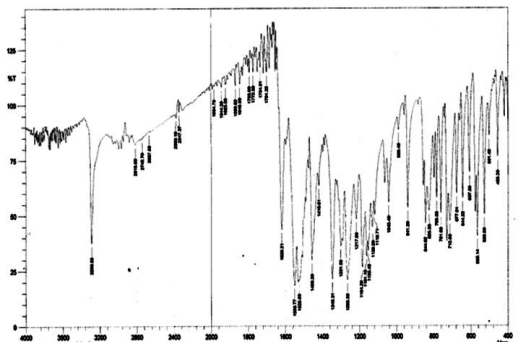


Figure 2: Calibration curve for Deferasirox

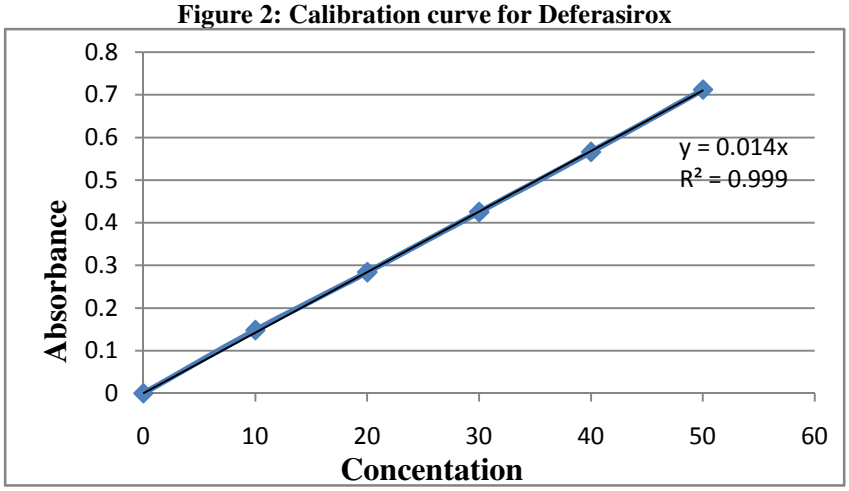


Table 2: Pre-compression parameters for formulations F-1 to F-9

Formulations	Angle of repose	Compressibility Index (%)	Hausner's ratio
F-1	42	23.32	1.43
F-2	31.22	18.54	1.21
F-3	21.21	16.22	1.20
F-4	26.87	19.54	1.25
F-5	36.43	18.23	1.23
F-6	31.21	21.23	1.32
F-7	23.56	14.02	1.18
F-8	22.87	13.32	1.11
F-9	24.62	15.31	1.21

Table 3: Evaluation of Deferasirox oro dispersible Tablets

Formulation Batches	Hardness (kg/cm^2)	Thickness (mm)	Avg. weight (mg)	LOD (%)	Friability (%)
F-1	4.1±0.6	4.90±0.02	947.6±2.3	2.21	1.34
F-2	3.8±0.4	4.48±0.04	903.1±1.6	1.54	1.51
F-3	5.4±0.1	4.33±0.03	899.2±2.4	2.02	0.42
F-4	5.5±0.3	4.25±0.07	899.0±1.4	1.32	0.67
F-5	5.4±0.2	4.58±0.05	902.7±0.9	1.87	0.53
F-6	5.7±0.5	4.36±0.04	903.0±1.5	1.22	0.76
F-7	5.8±0.4	4.40±0.07	905.0±0.6	1.11	0.32
F-8	5.8±0.3	4.42±0.02	901.4±0.7	1.12	0.21
F-9	5.8±0.2	4.35±0.05	904.0±0.9	1.32	0.32

Table 4: Disintegration time, Dispersion time, Water content & Assay of all Formulations

Formulation	Disintegration time (sec)	Dispersion time (sec)	Water content (w/w)	Assay (%)
F-1	33±0.8	82±3.2	3.5	88.8
F-2	48±1.3	69±1.5	3.3	87.9
F-3	60±2.2	97±1.8	3.2	86.4
F-4	48±1.8	91±1.5	4.0	89.3
F-5	54±0.5	123±0.6	3.9	73.6
F-6	67±1.6	98±1.5	3.9	91.4
F-7	43±2.1	84±1.3	4.0	97.2
F-8	34±1.2	75±1.9	3.2	98.3
F-9	38±2.3	63±2.1	3.8	97.4

Assay (By HPLC method)

Figure 3: Assay Chromatogram for F-8 formulation

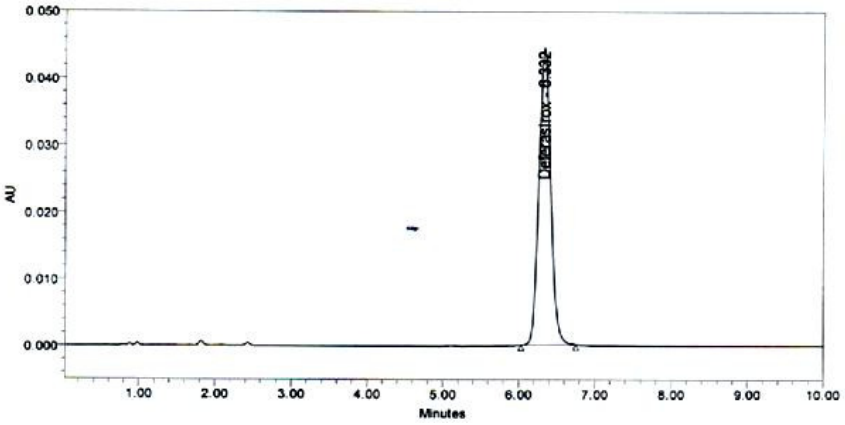


Table 5: Suitability report for Chromatogram

Compound	Retention time	Area /response	USP tailing factor	Theoretical plates	% RSD
Deferasirox	6.328	Sample-206348 Standard-464284	1.1	1897	0.23 n-=6

Figure 4.1: Dissolution profile of formulations F1-F4 compared with Innovator

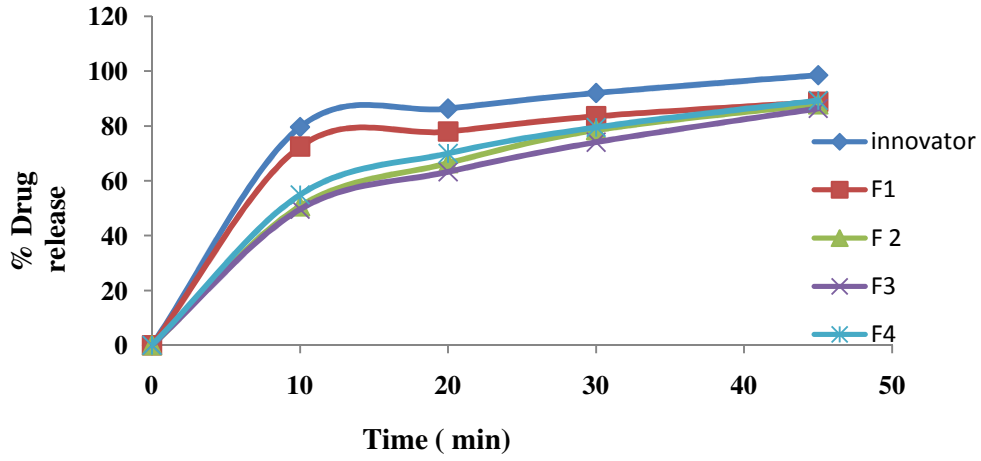


Figure 4.2: Dissolution profile of formulations F5-F9 compared with Innovator

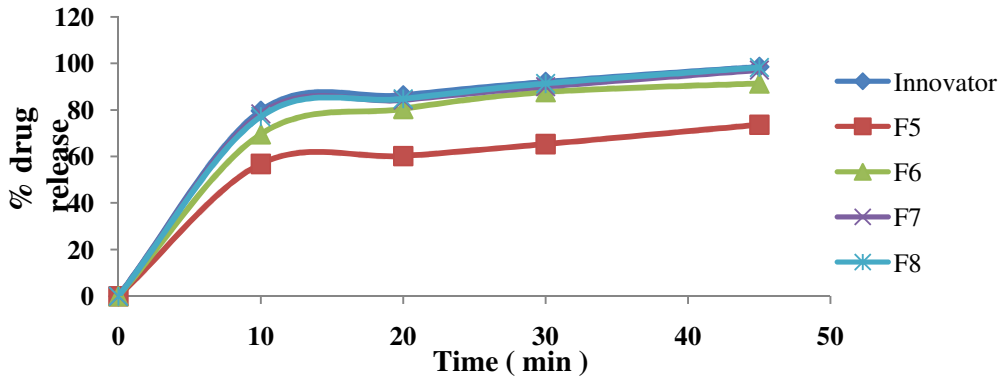


Figure 4.3: Dissolution profile of optimized formulation (F-8) compared with Innovator

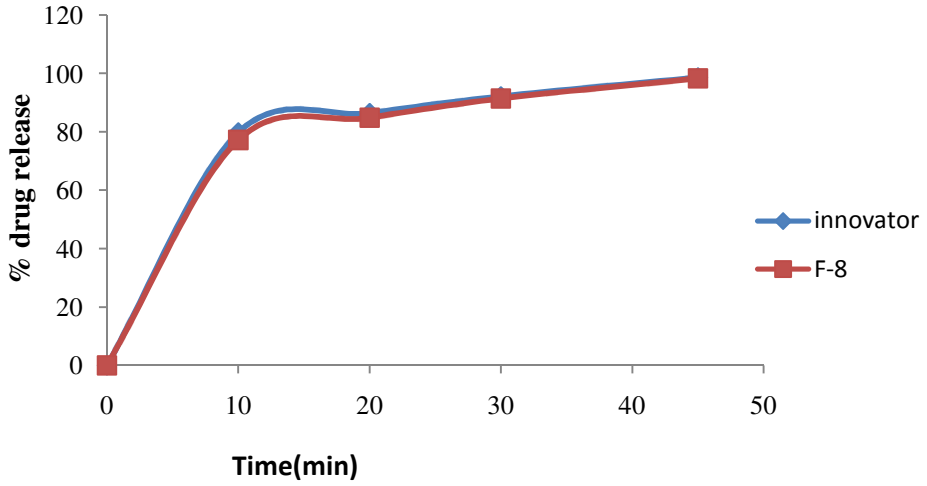
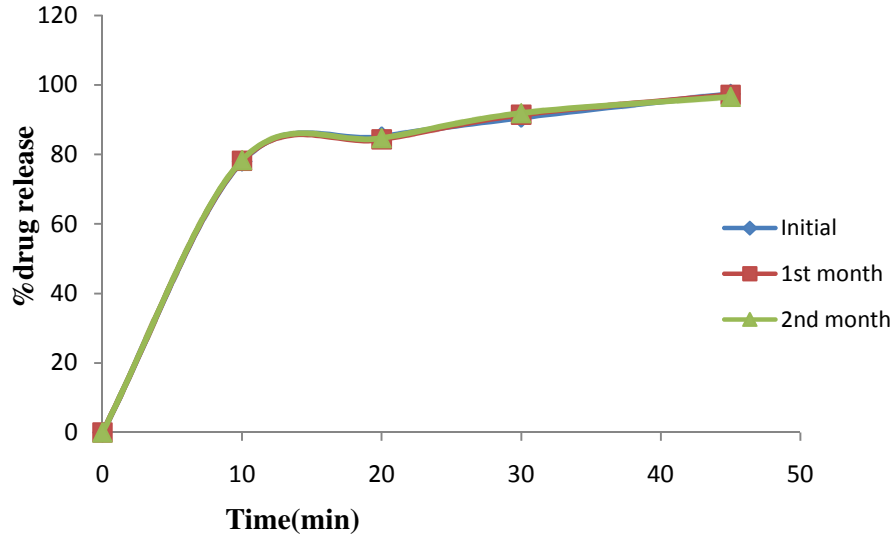


Table 6: Physical and chemical parameters of Deferasirox dispersible tablets (F-8) after 1st and 2nd month at 40±2°C /75±5 %RH (Packing: HDPE Bottle)

Parameter	Initial	1 Month	2 Month
Description	Light orange coloured round shaped uncoated tablets	No change	No change
Avg. wt (mg)	903.0±0.7	903.2±0.9	903.4±0.4
Hardness (kp)	5.89±0.3	5.83±0.5	5.77±0.3
Thickness (mm)	4.41±0.02	4.48±0.04	4.53±0.3
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 5: Graphical representation of Dissolution profiles of stability studies conducted at 40±5°C /75±5 %RH for formulation 8



compared to other formulations. The disintegration time

(34 sec), dispersion time (75 sec) and percentage of drug release (98.3 %) were found to be satisfactory and it matches with the innovator. So, the batch size was increased in further trial to check the reproducibility (Formulation *9*).

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