

PREPARATION AND *IN VIVO* EVALUATION OF POORLY SOLUBLE DEFERASIROX DISPERSIBLE TABLETS BY HYDROXY PROPYL BETA CYCLODEXTRIN COMPLEXATION

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ABSTRACT

Objectives: The objective of the present investigation was to prepare dispersible tablets of Deferasirox, using various super disintegrants. Deferasirox is novel tridentate oral chelator indicated in the treatment of Chronic Iron Overload due to blood transfusions in adult and paediatric patients. The aim of the study was to enhance safety and efficacy of drug molecules and to achieve better patient compliance among paediatric and geriatric patients by avoiding the difficulty in swallowing.

Methods: Tablets were prepared by wet granulation method using Sodium starch glycolate, Crospovidone XL and Hydroxy propyl cellulose (L-HPC) as super disintegrants. The tablets were evaluated for weight variation, mechanical strength, *in vitro* dispersion time, *in vitro* disintegration time, *in vitro* drug release characteristics and *in vivo* efficacy.

Results: Hardness and friability data indicated good mechanical strength of tablets. *In vitro* dispersion results showed that the tablets exhibited a rapid dispersion within 3 min (61- 92 s). *In vitro* disintegration time results were found to be in the range of 39.16 s and 79.6 s. The dissolution rate was found to increase linearly with increase in the concentration of superdisintegrant. The optimized formulation F8 containing 100 mg (11.11 % w/w) crospovidone showed better and faster drug release compared to marketed product. The optimized formulation F8 decreased the serum iron levels nearly to the normal range in *in vivo* efficacy study.

Conclusion: It was concluded that super disintegrants addition technique is a useful method for preparing dispersible tablets by wet granulation method.

Keywords: Complexation, Cross povidone XL, Oral chelator, Super-disintegrant.

INTRODUCTION

Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed as a whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated [1].

The advantages of this dosage form are manifold: tablets are cost effective to manufacture, convenient to dispense and store, and easy for the patient to administer and they provide a versatile means of delivering the drug.

Despite all the advantages, conventional tablets generally do not prove useful in certain situations. The elderly face difficulties in taking conventional oral dosage forms (which is solutions, suspensions, tablets, capsules) because of hand tremors and dysphagia [2]. Swallowing problem is also common in young individuals because of their under developed muscular and nervous system. Other groups that may experience problems using conventional oral dosage form include mentally ill, developmentally disabled patients, and patients who are uncooperative or who are suffering from severe nausea [3, 4].

Dispersible tablets as defined in Ph. Eur. are uncoated or film coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. Dispersible tablets are required to disintegrate within 3 minutes in water at 15-25 °C. Also the dispersion produced from a dispersible tablet should pass through a sieve screen with a nominal mesh aperture of 710 microns. The dispersion properties of dispersible tablets can be facilitated by the inclusion of an acid/base couple in which the base liberates carbon dioxide when the components of the couple are dissolved in water [5].

The Dispersible tablets are mainly based on the principle of employing superdisintegrants in their formulation which at low

concentrations, facilitate quick disintegration of the tablets. An ideal disintegrant should have poor solubility, poor gel formation, good hydration capacity, good compressibility, flow properties and no tendency to form complexes with the drugs [6, 7].

They are more convenient for active pharmaceutical ingredients with insufficient stability in water. Easy handling, accurate dosing, small packaging size and minimal risk of suffocation make them more beneficial for children, elderly and schizophrenic patients who have difficulty in swallowing conventional solid dosage forms [5]. Patients with myelodysplastic syndromes, sickle cell disease, β -thalassemia, Diamond-Blackfan syndrome, and other rare anaemia who require repeated blood transfusions as supportive therapy are at risk of developing iron overload with each additional unit of blood they receive. For years, the only method available of reducing transfusional hemosiderosis was weekly, prolonged subcutaneous or intravenous injections of the iron chelator deferoxamine [8].

Deferasirox is a new once-a-day oral iron chelating agent (selective for iron as Fe^{3+}) for iron overload in patients 2 years of age and older that was approved by the US Food and Drug Administration in November 2005. It is a tridentate ligand that binds to iron with high affinity in a 2:1 ratio. It works in treating iron toxicity by binding trivalent (ferric) iron (for which it has a strong affinity), forming a stable complex which is eliminated via the kidneys. Deferasirox is practically insoluble in water, freely soluble in Dimethyl formamide, Dimethyl sulfoxide and slightly soluble in methanol. The absolute bioavailability (AUC) of Deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The mean elimination *half life* ranged from 8 to 16 hours following oral administration [5, 9]. The problems associated with Deferasirox oral tablets are high hydrophobicity, longer elimination *half life*, high protein binding & poor aqueous solubility which reduces the complete-bioavailability. Therefore, the present work involves formulation and development of Deferasirox dispersible tablets to deliver optimum concentration of drug at desired site at specific time.

MATERIALS AND METHODS

Materials

Deferasirox was obtained as a gift sample from MSN laboratories, Hyderabad. Hydroxypropyl β cyclodextrin was purchased from Hi-Media (Mumbai), Crospovidone XL from Ansul agencies (Mumbai), Povidone K30 and MCC from Signet Chemical Corporation (Mumbai). All the other chemicals used were of analytical grade.

Preformulation studies

Compatibility studies

Compatibility studies were carried out by mixing the pure API with various excipients in different proportions. Studies were carried out by mixing definite proportions of drug and excipient and kept in glass vials, which were stored at 55 °C (2 weeks) and 40 \pm 2 °C/75 \pm 5 % RH (4 weeks). Physical observations of the blend were recorded at regular interval of one week [10].

Compatibility of the Deferasirox with polymers, superdisintegrants and excipients was established by infrared spectral analysis.

Preparation of inclusion complex of Drug- HP β CD

Inclusion complex of Deferasirox and HP β CD (in formulations F3-F9) was prepared in ratio of 1:1 by kneading method. In this method, the required quantities of HP β CD and distilled water were mixed together in a mortar to obtain a homogeneous paste. Deferasirox was then added slowly. A small quantity of methanol was added to assist the solubility of Deferasirox. The mixtures were then ground for 1 h. During this process, an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. The paste was dried in an oven at 45-50 °C for 24 h. The dried complexes were pulverized and then sieved through a #100 sieve [11].

Preparation of Tablets

Dispersible tablets containing 250 mg of Deferasirox were prepared by direct compression method and wet granulation methods. The various formulae used in the study are shown in Table 1.

Table 1: It shows the Composition of Deferasirox Dispersible Tablets

S. No.	Ingredient	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1	Deferasirox	250	250	501.2	501.2	501.2	501.2	501.2	501.2	501.2
2	Lactose monohydrate	244	97	-	-	-	-	-	-	-
3	Crospovidone XL	50	25	30	35	-	50	100	100	100
4	MCC pH 102	300	-	-	-	-	-	-	-	-
5	MCC pH101	-	333.5	307.3	302.3	252	257.3	304.3	290.8	290.8
6	Starch 1500	30	-	-	-	-	30	30	30	30
7	Povidone K30	-	25	45	45	45	45	45	45	45
8	SSG	-	-	-	-	42	-	-	-	-
9	L-HPC-LH11	-	-	-	-	34	-	-	-	-
10	Tween 80	-	-	-	-	4	-	-	-	-
11	SLS	6	6	6	6	-	6	6	6	6
12	Sucralose	-	-	-	-	-	-	-	8	8
13	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
14	Aerosil	10	9	9	9	9	9	9	9	9
15	SSF	-	-	-	-	6	-	-	-	-
16	Talc	-	-	-	-	6.8	-	-	-	-
17	Flavour	-	-	-	-	-	-	-	5	5
18	Magnesium stearate	10	4.5	4.5	4.5	-	4.5	4.5	4.5	4.5

*Formulations F2-F9 Drug-HP β CD complex was taken, All the ingredients were taken in mg

In direct compression method (F1), all the ingredients except Aerosil and Magnesium stearate were weighed and passed through #40mesh, then mixed for 2 min uniformly in a blender followed by pre lubrication with Aerosil for 5 min and then lubricated with Magnesium stearate.

In the wet granulation method (F2-F9), all the ingredients were weighed accurately and mixed thoroughly (except magnesium stearate and Aerosil). Then the above mixture was granulated using binder solution. Granules were prepared by passing the wet mass through #18mesh. Prepared granules were dried in hot air oven at 45 °C. The dried blend was passed through #18mesh and then pre lubricated using Aerosil for 5 min and then lubricated with Magnesium stearate in blender for 2 min.

Formulation F5 was made by using a new formula i.e., Hydroxy propyl cellulose (L-HPC-LH11), SSG, Magnesium stearate, Talc and SSF. The binder solution was prepared by dispersing Povidone K30 and Tween 80.

In formulations F2-F4, the superdisintegrant was added extra granularly whereas in formulations F6-F9, the superdisintegrant was added both intra and extra granularly.

The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio [12]. After evaluation of powder blend, the tablets were compressed with a ten-station rotary punch-tabletting machine (Rimek Mini Press-1) using 15 mm flat punches set.

Evaluation of Formulated Tablet

The various formulations were evaluated for hardness, thickness, weight variation, friability, *in vitro* dispersion time, *in vitro* disintegration time, uniformity of dispersion, drug content/ content uniformity, *in vitro* dissolution studies and *in vivo* efficacy studies.

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 [12].

2.5.1 Hardness

Schlunzier hardness tester (Dr. Schleuniger Pharmatron, USA) 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/cm² [13].

2.5.2 Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital Vernier scale (Mitutoyo, Japan) and the average thickness was determined in mm [13].

2.5.3 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 % or less is desirable. If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. The test was carried out using the Roche friabilator (Electrolab, Mumbai). The tablets were dedusted and reweighed [12].

The tablets that lose less than 1 % weight were considered to be compliant.

The percentage weight loss in tablet was determined using formula.

$$F = \frac{W_{\text{Initial}} - W_{\text{Final}}}{W_{\text{Initial}}} \times 100$$

Drug content uniformity

According to U.S.P, Ten tablets were randomly taken and triturated using glass mortar and pestle. The blend equivalent to 40 mg of drug was weighed and dissolved in 250 mL of phosphate buffer pH 7.4 containing 0.5 % w/w Tween 20. The drug was allowed to dissolve in the solvent, the solution was filtered and 1 mL of filtrate was taken in 10 mL of volumetric flask and diluted up to the mark with phosphate buffer pH 7.4 containing 0.5 % w/w Tween 20 and analyzed spectrophotometrically at 267 nm. The amount of Deferasirox was estimated by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each batch of formulation [14].

Test for Uniformity of dispersion

This test is 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) [14].

In vitro Dispersion time

In vitro dispersion time is measured by the time taken to form uniform dispersion. It is an unofficial parameter applicable only to dispersible tablets. In this method, tablet was added to 10 mL of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and dispersion time was noted.

In vitro Disintegration studies

Disintegration time is the time required for a tablet to break into granules of specified size (or smaller), under carefully specified test conditions. The disintegration test was 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 was performed to ensure disintegration of tablets in water, if it is to be used as a dispersible tablet. Dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets as per the compliance in the Indian Pharmacopoeia [14].

In vitro Dissolution studies (By UV method)

The *in vitro* dissolution study was carried out in the USP- Type II dissolution test apparatus (paddle). One tablet was placed in each of the six dissolution flasks containing 900 mL of dissolution medium, previously maintained at 37 ± 0.5 °C.

After completion of each specified time interval, 2 mL 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 preparation. Finally the percent drug dissolved from Deferasirox tablets was calculated.

In vivo efficacy study

Male Wistar rats were grouped under test, negative control and control of 6 animals each. In negative control and test groups, iron-overload was induced by 5 doses (one dose every two days) intraperitoneal injection of 60 mg/kg iron-dextran-saline. The control rats received the same volume of saline. Similarly stock solution of Deferasirox tablets of 2.5 mg dose was prepared and orally administered to the test group using flexible plastic tube attached to stainless steel gavage once a day for 7 days. At the end of 7 days, blood was withdrawn through the retro-orbital plexus and serum iron was estimated using Iron-TIBC kit (Coral Clinical Systems, Goa). The protocol was approved by Institutional Animal Ethical Committee constituted for the purpose as per CPSCEA guidelines. Results were expressed as mean \pm SD and statistical significance was determined using analysis of variance followed by Tukey's Multiple Comparison Test using GraphPad Prism 5 software [15].

Stability studies

The final formulation was packed in suitable packing like blister and strip packs and then kept at different temperature and humidity conditions and the samples were analyzed for their physical and chemical properties. The formulation was subjected to an accelerated testing at 40 ± 2 °C and 75 ± 5 % RH for 3 months. After every 30 days, ~~time interval~~ the tablets were analyzed for drug content uniformity, friability, hardness, thickness, uniformity of weight, *in vitro* disintegration time and % drug release for up to 90 days [16].

RESULTS AND DISCUSSION

Preformulation studies

For each designed formulation, blend of drug and excipients was prepared and evaluated for micromeritic properties as shown in Table 2. The preformulation studies of blend of Formulation F1 showed very poor flow properties. Hence, wet granulation method was chosen for further study

Table 2: It shows the Micrometric Properties of Mixed Blend and Excipients

Formulation code	Bulk density (g/cm ³) (Mean \pm SD)	Tapped density (g/cm ³) (Mean \pm SD)	Hausner's ratio (Mean \pm SD)	Compressibility index (Mean \pm SD)	Angle of repose(°) (Mean \pm SD)
F1	0.329 \pm 0.0012	0.37 \pm 0.002	1.124 \pm 0.008	11.11 \pm 0.759	36.6 \pm 1.222
F2	0.342 \pm 0.0018	0.383 \pm 0.005	1.12 \pm 0.014	10.59 \pm 1.087	29.38 \pm 0.895
F3	0.346 \pm 0.0029	0.379 \pm 0.008	1.09 \pm 0.017	8.67 \pm 1.348	28.02 \pm 2.074
F4	0.348 \pm 0.0012	0.382 \pm 0.003	1.086 \pm 0.020	8.71 \pm 0.780	26.71 \pm 0.569
F5	0.337 \pm 0.0017	0.368 \pm 0.003	1.09 \pm 0.004	8.40 \pm 0.380	26.25 \pm 0.573
F6	0.339 \pm 0.0012	0.375 \pm 0.002	1.107 \pm 0.004	9.23 \pm 0.395	26.09 \pm 0.755
F7	0.349 \pm 0.0049	0.384 \pm 0.003	1.103 \pm 0.009	9.18 \pm 0.815	26.25 \pm 0.433
F8	0.340 \pm 0.0012	0.368 \pm 0.003	1.082 \pm 0.005	7.39 \pm 0.520	25.56 \pm 0.395
F9	0.339 \pm 0.0020	0.367 \pm 0.004	1.083 \pm 0.008	7.6 \pm 0.704	25.39 \pm 0.356

*Values expressed as a mean of triplicate \pm SD

FTIR study

The IR spectra of pure drug Deferasirox, drug and HP β CD complex and formulation showed similar peaks at their respective wavelengths with minor differences. All the important functional group frequencies for Deferasirox (phenolic OH peak at 3226 cm⁻¹

CN stretching at 1666 cm⁻¹, C=C stretching at 1512 cm⁻¹ and carboxylic OH stretching at 2546 cm⁻¹) were present in the spectral peaks of the complex and formulations indicating compatibility of drug with HP β CD and formulation excipients. The compatibility studies revealed that all the excipients were compatible with the drug.

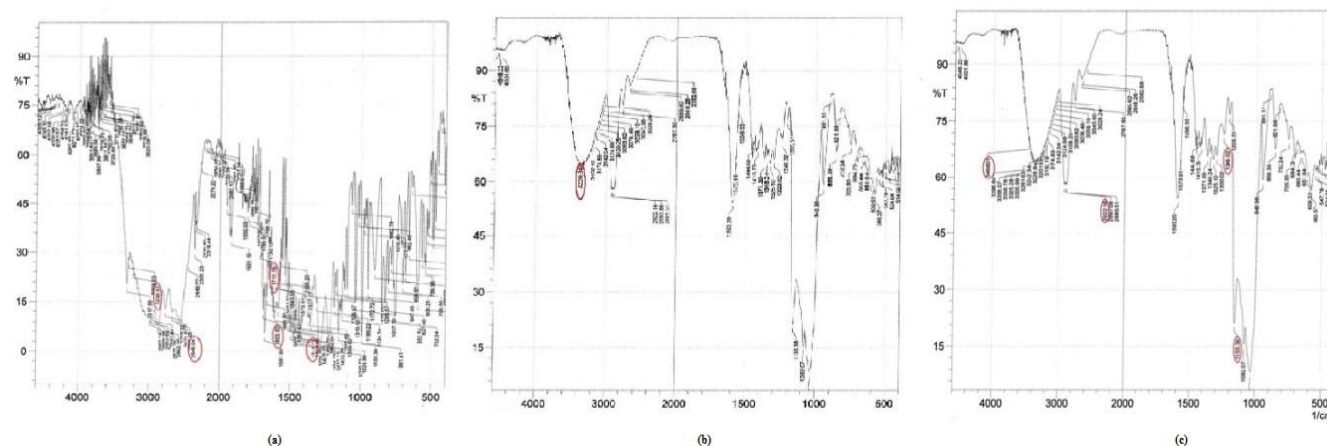


Fig. 1: It shows the FT-IR spectra of pure drug, complex and formulation F8

Post-compression parameters

Physical appearance

Formulated tablets of dispersible tablets were round in shape, 15 mm in diameter, with a flat surface and good physical appearance.

Thickness

The thickness of the formulated tablets was found to be in the range of 5.271 ± 0.008 mm to 5.45 ± 0.029 mm as reported in Table 3.

Table 3: It shows the Parameters Evaluated and Data Obtained for Deferasirox Dispersible Tablet Formulations

Formulation code	Weight variation (n=20)(%) (Mean ±SD)	Uniformity of thickness (n=20)(mm) (Mean ± SD)	Hardness (n=10) (kg/cm ²) (Mean ± SD)	Friability (%) (n=10) (Mean ±SD)	Drug Content* (%) (Mean ± SD)
F1	1.013±0.678	5.45±0.029	1.701±0.089	1.213±0.091	97.2±0.883
F2	1.00±0.483	5.315±0.011	2.34±0.119	1.112±0.015	97.9±1.067
F3	0.9991±0.077	5.314±0.016	4.19±0.016	0.816±0.036	96.8±0.374
F4	0.9995±0.077	5.309±0.008	4.169±0.025	0.726±0.04	97.5±0.489
F5	0.9997±0.216	5.281±0.011	4.159±0.042	0.61±0.028	93.8±0.509
F6	1.001±0.306	5.271±0.008	4.166±0.048	0.48±0.035	97.5±0.616
F7	899.69±0.371	5.296±0.011	4.126±0.01	0.523±0.038	98.2±0.432
F8	899.71±0.325	5.316±0.008	4.136±0.025	0.36±0.041	98.6±0.616
F9	899.83±0.209	5.305±0.007	4.183±0.013	0.45±0.029	98.8±0.374

*Values expressed as mean of triplicate

Test for Hardness

The hardness of F1 and F2 were 1.701 ± 0.089 kg/cm² and 2.34 ± 0.119 kg/cm² which were not satisfactory. Hardness of formulations F3 to F9 was found to be in the range of 4.126 ± 0.01 to 4.19 ± 0.016 kg/cm² as tabulated in Table 3. The obtained results revealed that the tablets of formulations F3-F9 showed good hardness.

Friability test

Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. Friability for the formulations (F3-F9) were found to be in the range of 0.36 ± 0.041 to 0.816 ± 0.036 which were <1 % which indicated that the dispersible tablets of F3-F9 formulations were within the I.P limits and possessed good mechanical strength [14].

The friability values of formulations F1 and F2 were >1 % (1.213 ± 0.091, 1.112 ± 0.015 respectively) indicating poor mechanical

strength. This may be attributed to the poor flow properties of the blend. The obtained results were tabulated in Table 3.

Weight variation test

In the weight variation test, the U.S.P limit for the percentage deviation of tablets having weight greater than 324 mg is ± 5 % [13]. All the tablets passed weight variation test as the % weight variation was within the limits of ± 5 %. It was found to be in the range of 0.990 % to 1.01 % as shown in the Table 3.

Content uniformity

The mean drug content carried out in triplicate was found to be in the range 93.8 ± 0.509 % to 98.8 ± 0.374 % given in Table 3.

Uniformity of dispersion Even though SSG was used as a super disintegrant, poor dispersion was occurred and the residue was retained on the sieve when it was passed through sieve no 22. In formulations F1-

F6, a small amount of substance was retained on the sieve while passing the dispersion through sieve no 22 which indicates that these batches fail the specific test for dispersible tablets. In order to overcome this, the concentration of superdisintegrants was gradually increased and the method of addition of superdisintegrants was also varied. The dispersed mixture from the batches F7-F9 passed freely from the sieve without leaving any residue indicating that these batches with the optimized concentration of superdisintegrants passed the test for uniformity of dispersion.

In vitro Dispersion time

Rapid dispersion within seconds has been observed in all the formulations. On the basis of de-aggregation time of the tablets,

according to the EP IV Ed., the formulations (F4-F9) developed can be defined as “fast dispersible”. The limit for de-aggregation was suggested as within 3 min. The values found to be obtained are mentioned in Table 4.

In vitro disintegration time

Internal structure of the tablets that is pore size distribution, water penetration into tablets and swelling of disintegrants are suggested to be the mechanisms of disintegration.

The results were found to be in the range of 39.16 ± 4.258 s and 79.6 ± 4.955 s tabulated in Table 4. All formulations showed disintegration time less than 180 sec which lies within IP specifications.

Table 4: It shows the *in vitro* Disintegration Time, Test for Uniformity of Dispersion and *in vitro* Dispersion Time for Formulations F1-F9

Formulation code	<i>In vitro</i> disintegration time (n=6)(s)(Mean ± SD)	Test for Uniformity of Dispersion*	<i>In vitro</i> Dispersion time (n=2) (s)
F1	79.6±4.955	Does not pass	71
F2	76.6±4.887	Does not pass	63
F3	78±4.203	Does not pass	118
F4	70.83±4.810	Does not pass	109
F5	69.6±3.992	Does not pass	125
F6	64.5±4.108	Passes	92
F7	42±4.83	Passes	65
F8	39.16±4.258	Passes	67
F9	39.5±3.149	Passes	62

*Values expressed as mean of triplicate

In vitro dissolution studies

The results obtained in the *in vitro* drug release for the formulations F1-F2, F3-F4, F5-F6, F7-F8, F9 and Marketed tablet were tabulated in Table 5. The plot of cumulative % drug release vs. time for the formulations F1-F2, F3-F4, F5-F6, F7-F8, F9 and Marketed tablet was depicted in Figure 2. The dissolution rate was found to increase linearly with increase in the concentration

of superdisintegrant and it was observed that the dissolution rate was more when the superdisintegrant was added both intra and extra granularly.

A comparative study of the formulation F8 with marketed product showed 98.03 % and 93.7 % drug release respectively at the end of 45 min. F8 formulation containing crospovidone showed better and faster drug release compared to marketed product

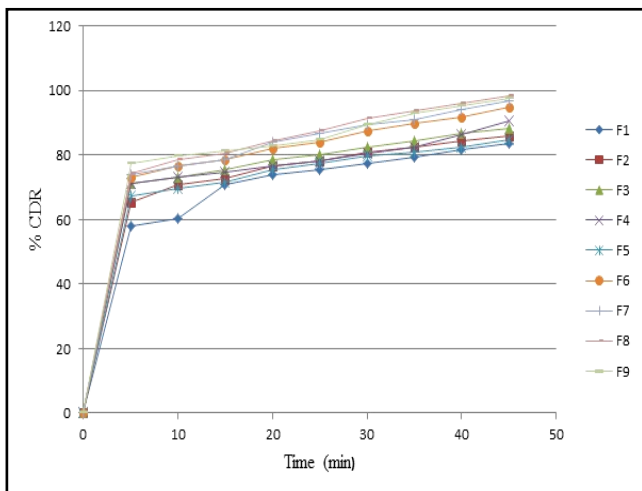


Fig. 2: It shows the *In vitro* dissolution profiles of the formulations F1-F9 in PBS pH 7.4 containing 0.5% Tween 20

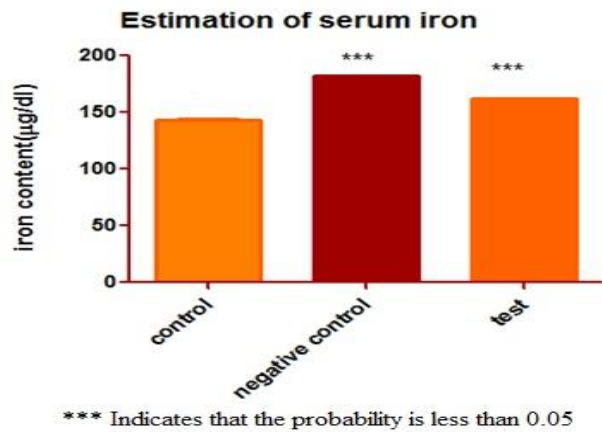


Fig. 3: It shows the *in vivo* serum iron levels in male Wistar rats

In vivo efficacy study

Formulation F8 decreased the serum iron levels nearly to the normal range. Results obtained were compared statistically with the control (without drug) by one-way ANOVA followed by Tukey's Multiple Comparison Test using GraphPad Prism5 software. Comparisons of negative control and formulation with the control by Tukey's multiple comparison test revealed that results obtained were statistically significant as $P < 0.05$ as shown in Figure 3.

3.1 Stability studies

The optimized formulation F8 was selected for stability studies. The formulations did not show much variation in any of the parameters. The results obtained were tabulated in Table 5. From these results it was concluded that, formulation F8 was stable throughout the period and retained its original properties.

Table 5: It shows the evaluation results after exposing Dispersible Tablets of Deferasirox (F8) for Accelerated storage conditions 40 ± 2 °C /75 ± 5 % RH for 3 months (Packing: Blister Pack)

Parameter	Initial	30 Days	60 Days	90 Days
Average wt (mg)	899.8	899.5	899.24	898.98
Hardness (kp)	4.22	4.15	3.8	3.75
Thickness (mm)	5.35	5.32	5.3	5.28
Friability (%)	0.20	0.23	0.26	0.28
Drug content (%)	98.6	98.38	98.12	97.8
<i>In vitro</i> disintegration time	39.32	39.64	40.5	41.2
<i>In vitro</i> dissolution rate at the end of 45 min	98.20	98.6	98.91	99.23

CONCLUSION

Deferasirox, indicated for the treatment of Chronic Iron Overload due to blood transfusions in adult and pediatric patients (aged 2 years and over) can be used to develop the dispersible tablet successfully, by wet granulation technique using selected superdisintegrants for the better patient compliance and effective therapy.

The tablets were found to be good without chipping, capping and sticking. Infrared spectroscopic studies indicated that the drug was compatible with the polymers selected for the formulation. In Formulation F1 (prepared by direct compression method), poor flow property was observed and also hardness and friability values were not satisfactory.

Formulations F2, F3, F4, F5, F6, F7, F8 and F9 were prepared by using wet granulation method. In Formulation F2, hardness was found to be less and the friability value does not comply with the specifications. Inclusion complex for enhancing solubility of Deferasirox was formed by using HPβCD in the molar ratio 1:1 by kneading method, confirmed by using FTIR. In Formulations F3, F4, F6 in order to get a better dispersion, the concentration of superdisintegrant was increased.

The prepared tablets disintegrated within few seconds; thereby enhance the absorption leading to its increased bioavailability. Disintegration time was found to be directly proportional to concentration of superdisintegrant used.

All the formulations were subjected to physicochemical analysis and out of them F8 was found to be satisfactory when compared to other formulations. Formulation F8 showed faster drug release in comparison to the marketed formulation. *In vivo* studies revealed that Formulation F8 decreased the serum iron levels nearly to the normal range. Accelerated stability studies for best selected formulation F8 showed physico-chemical stability for a period of 90 days at 40 °C ± 2 and 75 % RH.

Dispersible tablets of Deferasirox were prepared by wet granulation method using sodium starch glycolate, Croscopovidone XL and L-HPC as superdisintegrants. The tablets were disintegrated rapidly in oral cavity and had acceptable hardness and friability.

In vitro drug release from the tablets showed significantly improved drug dissolution. Hence it can be concluded that the superdisintegrant based dispersible tablets of Deferasirox would be quite effective a convenient dosage form aimed to achieve better patient compliance among paediatrics and geriatric population by avoiding the difficulty in swallowing. Further scope of the work can be focussed on long term stability studies and clinical evaluation.

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