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FORMULATION AND EVALUATION OF ORO DISPERSIBLE TABLETS OF DEFERASIROX

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ABSTRACT

Solid oral dosage forms are most convenient from patient as well as from manufacturing chemist's perspective. Dispersible tablets are required to disintegrate within 3 mins 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 objective of present study is to design and develop a stable solid oral dosage form of Deferasirox dispersible tablets by using Croscarmellose Sodium and MCC PH101 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.

KEYWORDS

Dispersible tablets, Deferasirox, Crosscarmellose sodium and MCC PH101.

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INTRODUCTION[1,2]

The oral route of administration still continue to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular dosage forms being tablets and capsules. Even few of the drawbacks of these dosage forms like swallowing and some drugs resist comparison in dense compacts, owing to their amorphous nature or flocculent, low-density characteristics. Drugs with poor wetting, slow dissolution properties, intermediate to large dosage,

and optimum absorption in the gastrointestinal tract or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.Solid oral dosage forms are most convenient from patient as well as from manufacturing chemist's perspective. They ensure uniformity of dosage, are more robust, have less microbiological issues compared to liquid dosage forms. However immediate release tablets cannot act as a substitute for suspension. Thus, there is a need for a formulation, which overcomes the problems associated with the swallowing of solid dosage forms and act as a viable substitute for suspensions. One such dosage form is dispersible tablet. 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. Typically a dispersible tablet is dispersed in about 5-15 ml of water (e.g. in a tablespoonful or a glass 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 mins 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.

Ideal Characteristics of Dispersible Tablets[3,4]

Dispersible tablets have the following ideal characteristics,

- They require water or other liquid at the time of administration.
- Should easily disintegrate and dissolve.
- Mask or overcome unacceptable taste of drug.
- They should have high drug loading.
- They should have pleasant feel in the mouth.
- They should have low sensitivity against environmental conditions like moisture, temperature etc.
- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- Should be portable without fragility concern.

They should be manufactured using conventional tablet processing and packaging equipment at low cost.

Different types of super disintegrants are used in the formulation of orodispersible tablets. The classification is showed in the Table No.1.

MATERIALS AND METHODS[5,6]

List of Chemicals

The chemicals are used in the formulation and evaluation of Deferasirox dispersible tablets are placed in the Table No.2.

List of Equipments

The equipments are used in the formulation and evaluation of Deferasirox dispersible tablets are placed in the Table No.3.

Formulation Development of Deferasirox Dispersible

Formulation of Deferasirox dispersible tablets carried out by direct compression method. The formula is showed in the Table No.4.

Method

Mix all the ingredients in geometrical proportion and the tablets were prepared by direct compression technique.

Evaluation Parameters

All the prepared tablets were evaluated for following official and unofficial parameters

- Weight Variation
- Thickness
- Hardness Test
- Friability Test
- Assay
- *In vitro* Release Study
- Physical appearance.

Dissolution study

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. For effective absorption of oral solid dosage form, simple disintegration of the dosage

form is not adequate and the dissolution of the drug into the surrounding medium plays a vital role. Though dissolution is not a predictor of therapeutic efficacy it can be looked upon a tool which can provide valuable information about biological availability of drug and batch to batch consistency. Dissolution is considered as one of the most important quality control tests performed for pharmaceutical dosage form. The results are displayed in the Table No.8 and 9.

Instrument

UV-Visible absorption spectrophotometer: The *in vitro* dissolution study was carried out in the USP dissolution test apparatus, type II (paddle).

Dissolution conditions: The following conditions are maintained for the dissolution of tablets.

Medium : pH 6.8 phosphate buffer
Volume : 900 ml
Temperature : 37°C ± 0.5°C
Apparatus : USP Type-II (Paddle)
rpm : 50
Time intervals **:** 10, 20, 30 and 45 mins

RESULTS AND DISCUSSION

Pre-compression parameters for formulations F-1 to F-9

The physical properties like bulk density, Tap density, Carr's Compressibility Index and Hausner's ratio are given in the following Table No.5.

The flow properties and other derived properties evaluated and proved to be within limits showing good flow properties.

Evolution of physical parameters for formulations F-1 to F-9

All 9 formulations were tested for Physical parameters like hardness, thickness, weight variation, friability. The results of the tests are Table No.6.

The prepared tablet formulations were evaluated for physic chemical parameters and were proved to be within limits.

DISCUSSION

The present investigation was undertaken to formulate Deferasirox into dispersible tablet for the treatment of chronic iron overload. For the development and formulation of dispersible tablets by direct compression technique was carried out with combination of various approved excipients. All the experimental formulation batches have been subjected to various evaluation parameters viz, average weight, thickness, hardness, friability, disintegration, uniformity of dispersion, dissolution studies, water content and assay.

Formulation F-1 to F-9 were carried out by direct compression method using ingredients such as Mannitol, Croscarmellose sodium, MCC PH 101, Starch 1500, SLS, Aerosil and Magnesium stearate. Here poor flow property was observed, hardness and friability values were also not satisfactory. The disintegration time were found to be 36 sec respectively. The percentage of drug release of F8 and F9 were found to be complying with that of the innovator product values. Of both F8 and F9, F9 shows better drug release so it is taken as best formulation.

Table No.1: Classification of super disintegrants

S.No	Structural type (NF name)	Description	Trade name (manufacturer)
1	Modified starches (Sodium starch glycolate, NF)	Sodium carboxymethyl starch; the carboxymethyl groups induces hydrophilicity and cross-linking reduces solubility.	Explotab®(Edward Mendell Co.), Primojel® (Generichem Corp.), Tablo® (Blanver, Brazil)
2	Modified cellulose (Croscarmellose, NF)	Sodium carboxymethyl cellulose which has been cross-linked to render the material insoluble.	AcDiSol® (FMC Corp.), Nymcel ZSX® (Nyma, Netherlands), Primellose® (Avebe, Netherlands) Solutab® (Blanver, Brazil)
3	Cross-linked poly-vinyl pyrrolidone (Cross povidone, NF)	Cross-linked polyvinylpyrrolidone; the high molecular weight and cross-linking render the material insoluble in water.	Crospovidone M® (BASF Corp.), Kollidon CL® (BASF Corp.), Polyplasdone XL (ISP Corp.)

Table No.2: List of chemicals

S.No	Ingredients	Manufacturer	Supplier
1	Deferasirox	ISP, Hyderabad	Chandra Lab, Hyderabad
2	Croscarmellose sodium	ISP Technologies Inc, USA	Ansul Agencies, Mumbai
3	Starch 1500	DMV International GmbH, Netherlands	KMV Enterprises, Hyderabad
4	MCC PH 101	FMC Biopolypmer, USA	Signet Chemical Corporation, Mumbai
5	SLS	Merck limited, Mumbai	Vasco Scientifics Pvt. Ltd., Secunderabad
6	Aerosil	Mayur Chemicals, Mumbai	Mayur Chemicals, Mumbai
7	Magnesium stearate	Ferro Industries Quimica, Portugal	Signet Chemical Corporation, Mumbai
8	Mannitol	DMV International GmbH, Netherlands	KMV Enterprises, Hyderabad
9	Aspartame	Firmenich Asia India Pvt.Ltd	Manish Global Industries, Chennai

Table No.3: List of equipment's

S.No	Equipment	Manufacturer
1	Electronic balance	Mettler-Toledo, USA
2	Bulk density apparatus	Electrolab, Mumbai
3	Rapid Mixer Granulator (RMG)	Anchor Mark Pvt. Ltd.,
4	Rotary Tablet punching machine	Rimek, Mumbai
5	Friability test apparatus	Electrolab, Mumbai
6	Tablet dissolution apparatus	Electrolab, Mumbai
7	Disintegration apparatus	Electrolab, Mumbai
8	Helium lamp (LOD)	Mettler-Toledo
9	Thickness (Vernier Calipers)	Mitutogo Vernier Calipers
10	Environmental Chambers	Thermolab
11	Hot air oven	Eltek motors, Mumbai
12	High performance liquid chromatography (HPLC)	Waters, Hyderabad
13	Sieves	Jayanth test sieves, Mumbai
14	Hardness tester	Dr.Schleuniger pharmatron, USA
15	Fluidized bed dryer	Anchor Mark Pvt. Ltd.,
16	Double beam spectrophotometer	Shimadzu. 1601, Japan
17	Fourier Transform Infra-Red Spectroscopy (FTIR)	FTIR-8001, Shimadzu, Japan
18	Stability chambers	Thermo lab

Table No.4: Formula for the preparation of Deferasirox Dispersible tablets

S.No	Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	*F-9
1	Deferasirox	250	250	250	250	250	250	250	250	250
2	Aerosil	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
3	Croscarmellose Sodium	25	50	25	25	25	25	25	50	50
4	MCC PH101	47.5	22.5	45	43.75	42.5	40	37.5	12.5	15
5	Starch 1500	25	25	25	25	25	25	25	25	25
6	Mannitol	125	125	125	125	125	125	125	125	125
7	SLS	-	-	2.5	3.75	5	7.5	10	10	7.5
8	Aspartame	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9	Magnesium stearate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Total weight		500	500	500	500	500	500	500	500	500

Table No.5: Pre-compression parameters for formulations F-1 to F-9

S.No	Formulation Code	Angle of repose (mean± SD)	Bulk Density(gm/cc) (mean± SD)	Tapped Density(gm/cc)(mean± SD)	Hausner's ratio (mean± SD)	Compressibility Index (%)(mean± SD)
1	F-1	25.80±0.25	0.645±0.03	0.769±0.023	1.06±0.05	20.40±0.03
2	F-2	20.32±0.32	0.588±0.015	0.666±0.015	1.03±0.07	20.26±0.15
3	F-3	25.70±0.64	0.625±0.025	0.714±0.065	1.02±0.03	20.74±0.21
4	F-4	24.28±0.91	0.76±0.069	0.872±0.45	1.13±0.01	20.20±0.28
5	F-5	22.16±0.69	0.689±0.035	0.78±0.020	1.15±0.03	18.23±0.32
6	F-6	20.34±0.25	0.555±0.016	0.625±0.089	1.11±0.05	17.50±0.35
7	F-7	26.59±0.32	0.714±0.075	0.833±0.064	1.15±0.07	13.00±0.39
8	F-8	25.26±0.64	0.748±0.042	0.868±0.078	1.14±0.03	12.26±0.45
9	F-9	25.12±0.72	0.749±0.016	0.868±0.082	1.13±0.06	12.44±0.52

Table No.6: Evolution of physical parameters for formulations F-1 to F-9

S.No	Formula	Weight Variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegration time (sec)	Assay (%)
1	F-1	502.6±0.13	3.97±0.03	5.02±0.11	0.28±0.04	29±0.32	99.8
2	F-2	504.1±0.45	3.52±0.31	5.13±0.07	0.29±0.02	38±0.38	98.3
3	F-3	497.2±0.16	3.31±0.23	5.48±0.14	0.22±0.05	52±0.43	101.0
4	F-4	501.0±0.21	3.27±0.08	5.52±0.16	0.29±0.01	59±0.47	99.5
5	F-5	505.7±0.17	3.60±0.16	5.44±0.04	0.20±0.03	63±0.56	100.7
6	F-6	503.0±0.32	3.38±0.12	5.79±0.02	0.21±0.04	51±0.59	98.1
7	F-7	502.0±0.45	3.36±0.31	5.85±0.11	0.23±0.02	32±0.33	99.7
8	F-8	503.4±0.21	3.43±0.08	5.80±0.14	0.23±0.01	35±0.29	100.2
9	F-9	503.0±0.35	3.41±0.35	5.89±0.17	0.20±0.04	34±0.21	99.98

Table No.7: Dissolution profiles of different formulations

S.No	Sampling Time (minutes)	Percentage of Cumulative Drug Release								
		F-1 % ± SD	F-2	F-3	F-4	F-5	F-6	F-7	F-8	*F-9
1	10	22.5	30.7	29.6	34.9	36.8	39.6	48.4	67.2	68.0
2	20	38.0	36.4	43.3	40.0	50.2	50.5	54.3	84.8	85.1
3	30	53.6	58.5	60.1	65.5	69.3	77.7	77.1	92.3	98.4
4	45	58.8	60.9	67.4	74.3	78.6	83.4	84.3	95.2	98.8

Table No.8: Analysis of *In vitro* Dissolution Study Parameters of Formulations

S.No	Formulation code	Zero order release		First order release		Higuchis classical diffusion	
		K_0	R^2	K_1	R^2	K_H	R^2
1	F1	1.318	0.959	0.020	0.980	9.220	0.988
2	F2	1.322	0.935	0.021	0.957	9.439	0.982
3	F3	1.466	0.955	0.025	0.986	10.37	0.994
4	F4	1.597	0.955	0.030	0.981	11.173	0.983
5	F5	1.684	0.952	0.034	0.992	11.975	0.996
6	F6	1.815	0.946	0.041	0.978	12.875	0.987
7	F7	1.746	0.920	0.040	0.980	12.740	0.988
8	F8	1.981	0.844	0.097	0.946	15.413	0.966
9	*F9	1.980	0.841	0.101	0.941	15.433	0.965

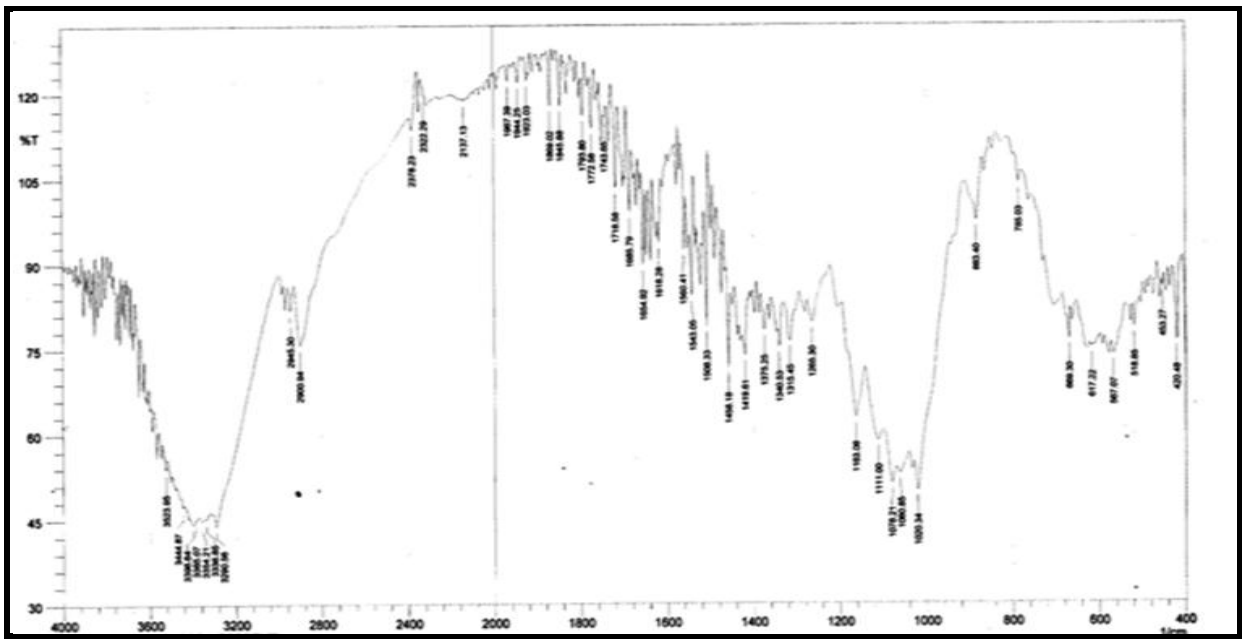

Figure No.1: FT-IR of Deferasirox

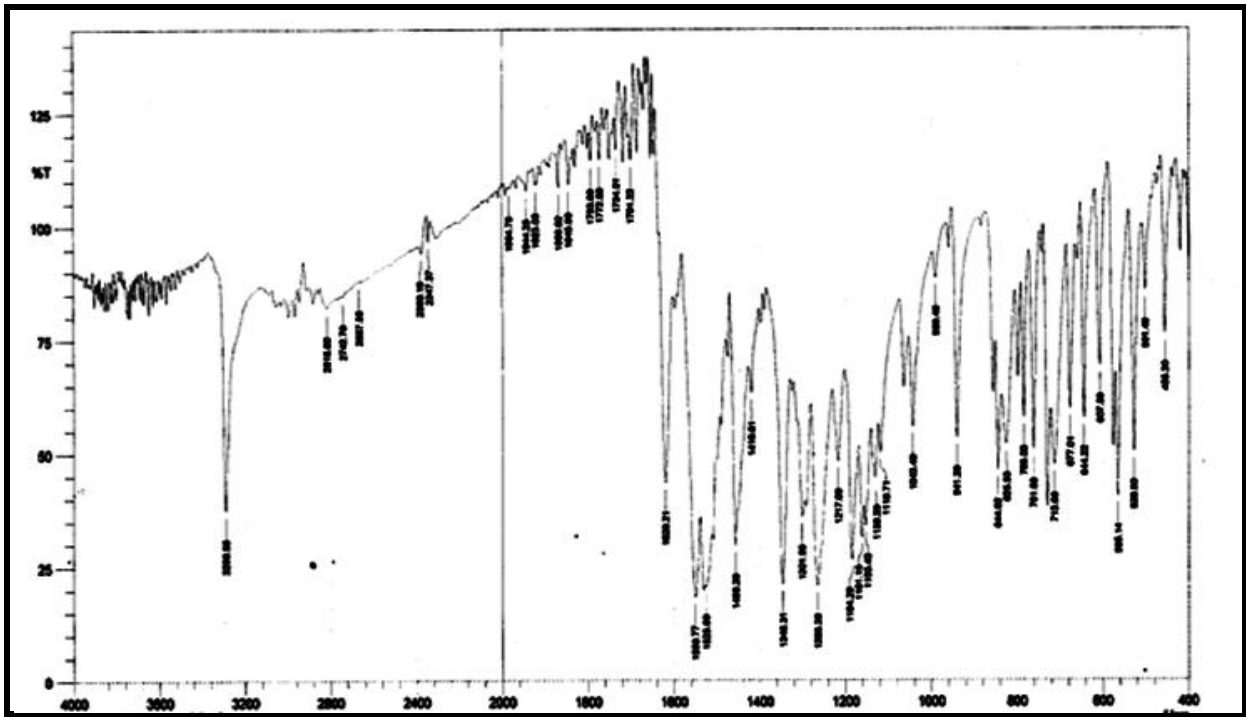

Figure No.2: FT-IR of Deferasirox+ Excipients

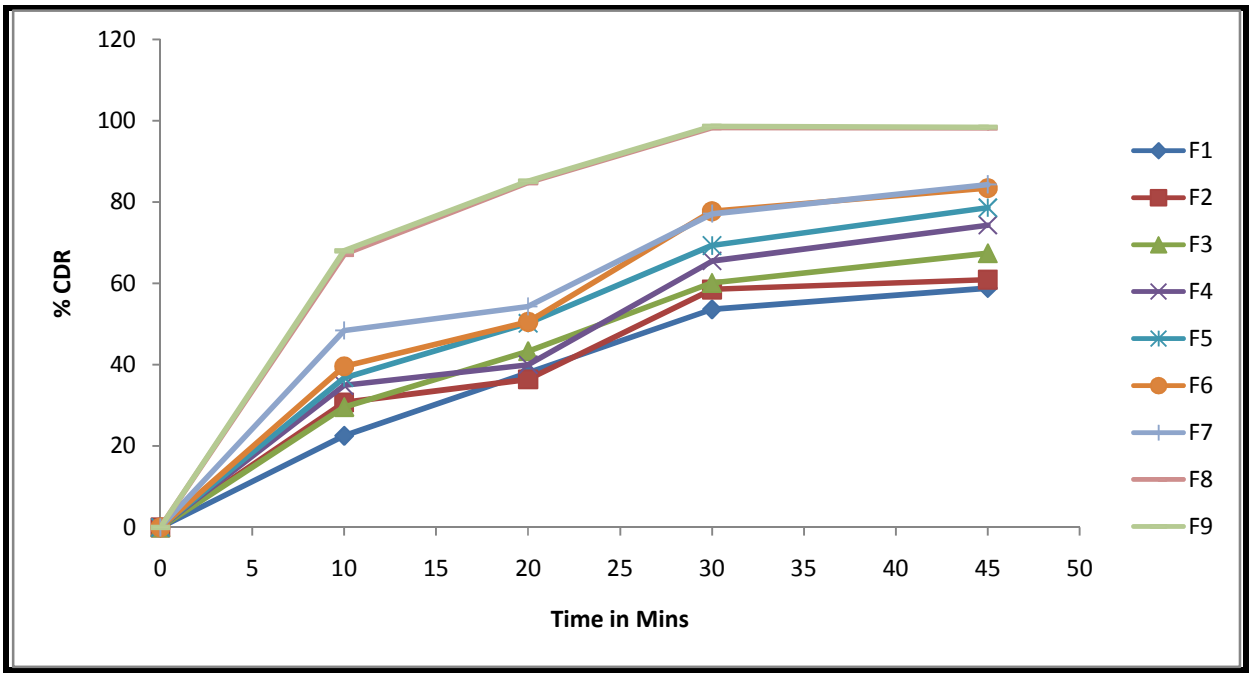

Figure No.3: *In vitro* dissolution profile of all formulations

CONCLUSION

All formulations 1, 2, 3, 4, 5, 6, 7, 8 and 9 was made by direct compression method. Pre compression and post compression parameters were evaluated. Best formulation was compared with that of the innovator and was found complying. The percentage of drug release of F9 was found to be complying with that of the innovator product values. So F9 is taken as the best formulation. Finally loaded for stability as per the ICH guidelines.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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