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Research Article

Preparation and evaluation of deferasirox effervescent release tablets

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ABSTRACT

Deferasirox is an oral iron chelater used to reduce chronic iron over load in patients who are receiving long term blood transfusion for condition such as beta-thalassemia. In this study deferasirox drug were formulated by direct compression. Six formulations of effervescent tablets were prepared by using different concentrations of effervescent agents to get desired release profile of reference product. Drug - Exciepient compatibility was studied by FT-IR spectral analysis. Effervescent tablets of deferasirox drug were prepared by using various excipients .Pre compressive parameters like carr's index of all formulations between 22.54 ± 0.1 to 11.68 ±0.19, indicates passable compressibility index. Angle of repose of formulations from 37.34±0.04 to 33.50 ±0.14 i.e.., it declares that all are possessing good flow properties and hausners ratio of all formulations was 1.29±0.09 to 1.12±0.10 which satisfies the limits of compressibility. Post compressive parameters like weight are within limits .Hardness test of all the formulations from 9.3± 0.13 to 10.3 ±0.45 kg/cm^2 .All the evaluation parameters were under acceptable ranges. The in vitro drug dissolution studies were carried out for the formulations in p^{H}6.8 phosphate buffer .Dissolution profiles of all trials were done among all the formulations F_6 better release. Stability studies were carried out for optimized formulation as per ICH guidelines.

Keywords: Deferasirox, Effervescent tablerts, FT-IR spectral analysis, Iron chelator

INTRODUCTION

Deferasirox tablets are iron chelating agents.

Pharmacokinectic properties

Bioavailability: 70%.
Protein binding: 99%.
Half life: 8-16 hrs.
Excertion: 8% through urine, 84% through feaces.

PHARMACODYNAMICS

Mechanism of action

Two molecules of deferasirox are capable of binding to 1atom of iron .Deferasirox works in treating iron toxicity by binding trivalents (ferric) iron (for which it has a strong affinity),forming a stable complex which is eliminated via the kidneys.

Defearsirox is iron chelating agent belonging to BCS class -2 having low water solubility and high intestinal permeability. The half-life of drug is 8-16 hrs.

Effervescent tablet is a tablet intended to be dissolved or dispersed in water before administration .Effervescent tablets are uncoated tablets that generally contain acid substances and carbonates or bicarbonates and which react rapidly in the presence of water by releasing carbon dioxide. They are intended to be dissolved or dispersed in water before use.

The objectives of work were proposed to be carried out in the following steps

To ultimate objective of the study was to formulate Deferasirox effervescent tablets to be used in the treatment of iron over load condition. Preformulation studies such as drug identity, physical, chemical properties and drug excipients compatibility. Formulation development of deferasirox effervescent tablets dosage form. To study formulation variables. To carry out in vitro studies of the optimized formulations. Stability studies as per ICH guidelines. Excipients used were Microcrystalline cellulose[1] , Crospovidone [2],Magnesium stearate[3] ,PVP-k30 ,Citric acid ,Sodium Bi-Carbonate, Mannitol .

PREFORMULATION STUDIES

The first step in rational development of dosage form of a drug substance is preformulations testing. It can be defined as investigation of physicochemical properties of drug substance alone and when combined with excipients.

Scope

To gather some useful information from preformulation studies for getting stable and bioavailable dosage forms. These studies are selective.

Goals of preformulation

- To establish physic chemical properties of new drug substance.
- To determine the kinetic rate profile.
- To establish its physical characters.
- To establish any compatibility issues.

API CHARACTERIZATIO

Description

Visual inspection of drug was done and description as per specification was checked

Organoleptic characteristics of drug

Properties	Observation
Organolepticproperties	Off white to white powder with unpleasant odour

Melting point

Melting point of drug was determined by capillary method. The melting point is found to be in the range of 269-270^{0}C the reported melting point for deferasirox was 269^{0}C.

Solubility

Drug was added to 10ml of media (i.e., simulated intestinal fluid 6.8pH) solubility in water.

Particle size determination

Flow characteristics of API

Bulk density gm/ml	Tapped density Gm/ml	Carr's Compressibility Index (%)	Hausners ratio	Angle of Repose (θ)
0.345±0.11	**0.511±0.01**	**32.48%±0.14**	**1.48±0.01**	**48.22±0.25**

Discussion

The flow property was poor for the pure drug.

Drug excipients compatibility studies

To establish drug –excipients compatibility , binary powder mixtures were prepared in 1:1

ratios with excipients . The binary mixtures were ground in a mortar , screened and the mixtures were filled individually in amber colored vials and sealed . After specific time period the mixtures were subjected to assay and all binary mixtures showed drug concentration ranges. FR-IR Spectrophotometric scanning was also done to establish drug – excipients –interactions .There was no evidence found about interactions of neither polymeric materials nor additives with drug.

Composition of API with different excipients used for compatibility studies

S.NO	Composition details	Ratio
1	Deferasirox	1:0
2	Deferasirox +Citric acid	1:1
3	Deferasirox +$NaHco_3$	1:0.5
4	Deferasirox +MCC	1:1
5	Deferasirox +Crospovidone	1:1
6	Deferasirox +Talc	1:1
7	Deferasirox +PVP K-30	1:1
8	Deferasirox+Magnesium stearate	1:0.5
9	Deferasirox +Mannitol	1:1

FORMULATION & EVALUATION

The main objective of this formulation development is to design the Deferasirox effervescent tablets i.e., the drug should be immediately released for a short period of time . In this formulation development, different batches are planned to formulate with different Effervescent release polymers in different ratios .

Preparation of Deferasirox effervescent tablets

The tablets were prepared by Wet granulation technique for F1 to F6 formulations.

Dry mix (premix)

- Sieve the drug through 40 # mesh and collect the shifted drug in butter paper.
- Sieve the dry-mix excipient through 40 # mesh and collect shifted excipient in butter paper .
- The sifted drug and the sifted excipients were mixed geometrically and thoroughly for10min in octagonal blender.

Pre-lubrication

Sieve the pre–lubricated excipients through 40# mesh and transferred into dry-mix both were mixed geometrically and thoroughly for 10min in octagonal blender

Lubrication

Sieve the lubricated excipient through 60# mesh. The powder mixture was lubricated with sifted magnesium stearate for 5min and the immediate tablets were compressed.

Compression

The tablets were compressed using compression machine with lubricated blend employing appropriate punch tooling (9mm concave punch). Collect the compressed tablets in to double poly lined bag

Formulation of deferasirox effervescent tablets

S.NO	Ingerdients	F1	F2	F3	F4	F5	F6
	Deferasirox	100	100	100	100	100	100
	Citric acid	100	110	120	130	140	150
	$NaHco_3$	150	150	150	150	150	150
	MCC	10	10	10	10	-	-
	CP	10	-	-	12	19	25
	PVP K-30	-	-	-	5	8	10
	Talc	5	5	5	5	5	5
	Magensium stearate	5	5	5	5	5	5
	Mannitol	120	120	110	83	73	55
	Core tablet (mg)	500	500	500	500	500	500

*All the values were expressed in mg per tablet

EVALUATION OF FORMULATED IMMEDIATE RELEASE TABLETS

Thickness[5]

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet– tablet uniformity.

Weight variation[6]

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Acceptance criteria for tablet weight variation

Average weight of a tablet (mg)	Percentage deviation (%)
130mg	±10
130-324mg	±7.5
More than 324	±5

Hardness[7]

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping.

Friability[8]

It is measure of mechanical strength of tablets. Roche friabilator is used to determine the friability. It is used for determining the percentage loss in weight of the tablets.

%Friability = (Initial weight – Final weight/Initial weight) ×100

%Friability of tablets less than 1% was considered acceptable.

Disintegration

The USP device to test disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly.

Invitro dissolution studies [9]

The dissolution test measure 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.

Dissolution conditions

Medium: 6.8 phosphate buffer
Volume: 900ml
Temperature: 37± 0.5°C
Apparatus: USP Type-II
Rpm: 50
Time intervals: 10, 15, 20

Procedure

Dissolution study conducted for optimized formulation using type-2 apparatus (ELECTROLAB). The dissolution test was performed with p^H 6.8 phosphate buffer as the dissolution medium at 50 rpm and at a temperature of 37ºC±0.5ºC for 60mins. A sample of the solution was withdrawn from the dissolution apparatus at different time interval of 10, 15,20,30,45, min and the sample volume was of fresh dissolution medium. Drug released were analyzed through UV spectrophotometer at 245nm.

RESULTS & DISCUSSION

Formulation development

Immediate release tablets of Deferasirox were prepared a total of 6 formulations were prepared and evaluated for pre compression parameters, Physic-chemical parameters and in vitro release studies.

Precompression parameters of Deferasirox blend

Blend characteristics of all formulations

Formulation code	Bulk density (gm/cc) ±SD*	Tapped density (gm/cc) ±SD*	Carr's index (%) ±SD*	Hausner's ratio ± SD*	Angle of Repose (°) ±SD*
F1	0.433±0.12	0.559±0.14	22.54±0.1	1.29±0.09	37.34±0.04
F2	0.439±0.02	0.554±0.04	20.75±0.02	1.26±0.01	38.13±0.06
F3	0.424±0.16	0.561±0.17	24.42±0.22	1.32±0.02	39.13±0.02
F4	0.431±0.09	0.559±0.11	22.89±0.13	1.29±0.03	38.33±0.65
F5	0.437±0.18	0.539±0.16	18.92±0.13	1.23±0.08	35.89±0.48
F6	0.442±0.11	0.543±0.13	18.60±0.19	1.22±0.05	38.38±0.66

*****represents mean ± S.D, n =3

Post compression studies

Physical parameters of all formulations

Formulation code	Hardness ($kgcm^2$) n =5±SD	Thickness (mm)n= 5±SD	Friability (%) n =10	Weight (mg)n= 20	Disintegration n =6(min)
F1	9.3 ± 0.13	4.31 ± 0.36	0.40 ± 0.09	320 ± 1.92	3.0 ± 0.15
F2	9.5 ± 0.18	4.30 ± 0.38	0.38 ± 0.04	319 ± 1.63	2.50 ± 0.12
F3	9.8 ± 0.25	4.28 ± 0.06	0.31 ± 0.07	319 ± 1.26	2.45 ± 0.20
F4	10.3 ± 0.54	4.27 ± 0.08	0.28 ± 0.02	318 ± 1.1	2.58 ± 0.05
F5	10.2 ±0.22	4.30 ± 0.07	0.22 ± 0.04	320 ± 1.35	2.46 ± 0.08
F6	10.4 ±0.39	4.31 ± 0.11	0.20 ± 0.08	320 ± 1.4	2.41 ± 0.25

Cumulative %drug release of F1 to F3 ±S.D*

Time (min)	F1	F2	F3
0	0	0	0
5	35.04±1.23	49.51±0.55	55.83±0.72
10	51.92±1.37	55.64±1.22	65.94±0.22
15	72.14±1.44	76.82±1.44	84.91±1.12
20	80.14±1.16	82.13±1.25	86.23±0.98
30	82.56±1.33	85.43±1.67	86.91±1.12
45	84.39±2.22	86.61±0.54	90.81±1.66
60	85.43±1.37	89.71±1.66	94.89±0.12

*represents mean ± S.D, n=6

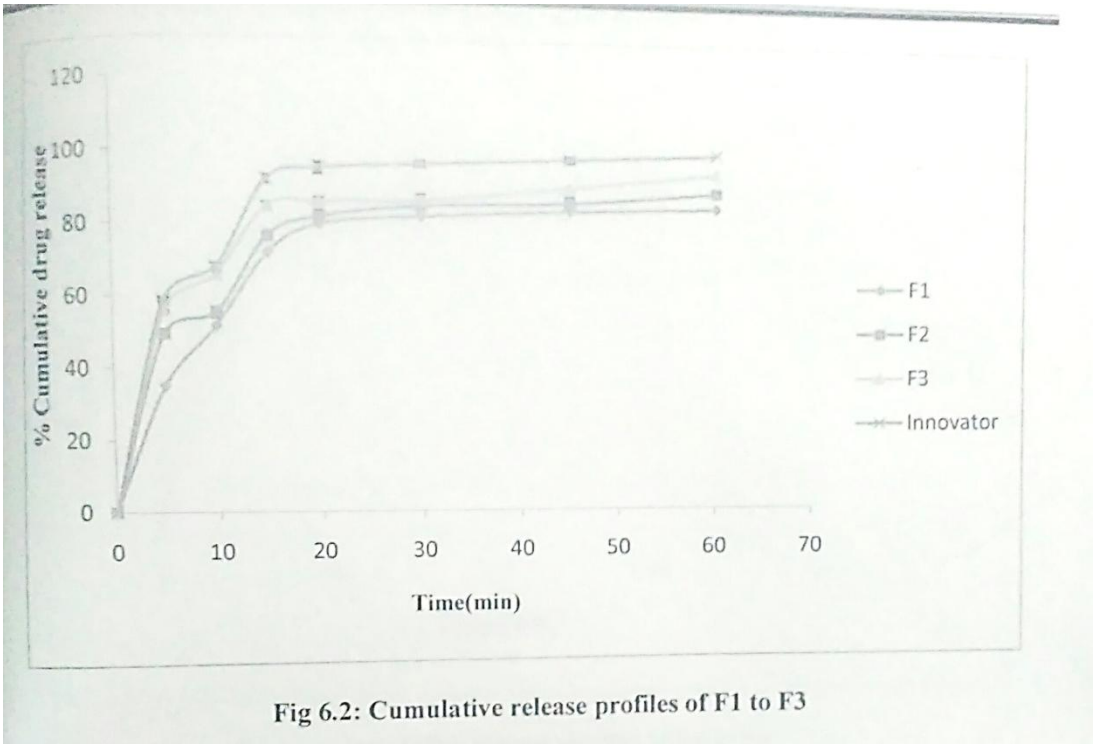

Fig 6.2: Cumulative release profiles of F1 to F3

Cumulative % drug release of F4 to F6 ± S.D*

Time (min)	F4	F5	F6
0	0	0	0
5	36.32±1.88	48.09±1.25	54.03±0.22
10	52.81±1.66	56.92±0.67	63.43±1.24
15	73.83±1.44	74.84±1.24	83.09±1.58
20	79.14±1.44	84.82±1.66	85.81±0.58
30	81.16±1.08	84.89±1.24	87.92±1.36
45	84.73±1.44	86.94±0.68	90.84±1.28
60	85.81±0.98	89.92±0.66	95.18±1.27

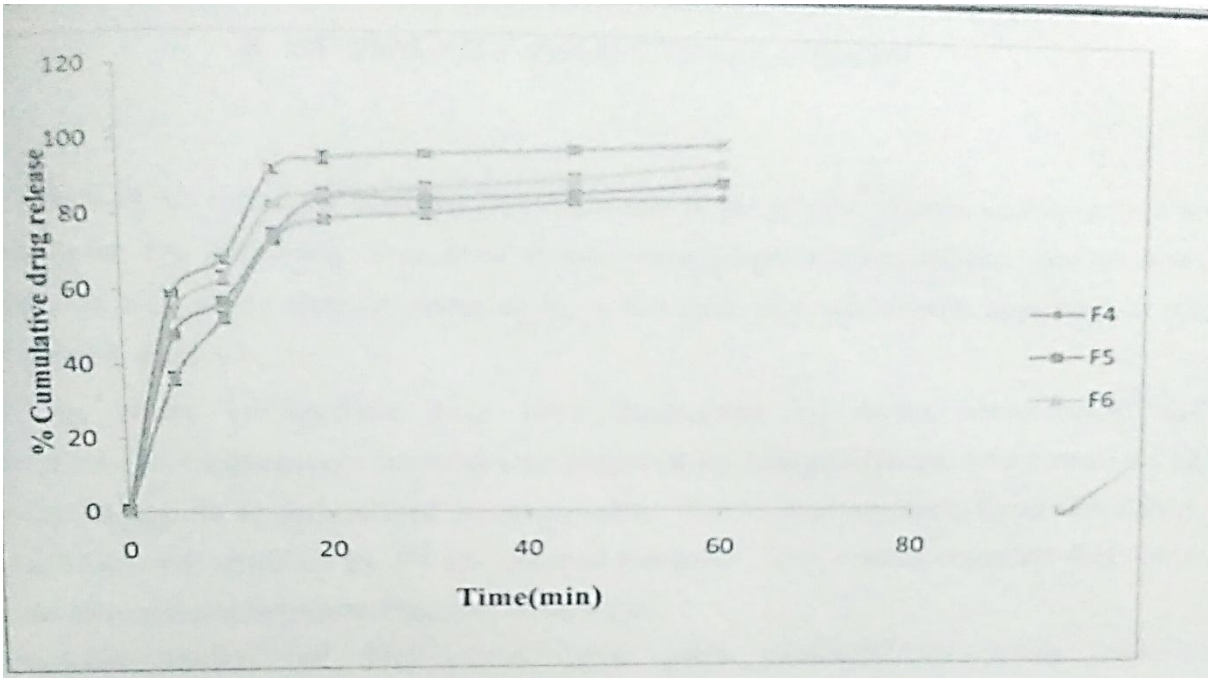

Fig 6.3: Cumulative release profiles of F4 to F6

*represents mean ± S.D, n=6

CONCLUSION

Deferasirox effervescent tablets were successfully prepared by using some selected effervescent agents to increase drug release by using direct compression method. All the prepared formulations were evaluated for both pre compressive and post compressive parameters , the values obtained were found to be satisfactory and they complies with pharmacopeial standards. The results generated in this study showed that the profile of drug release were the function of type and concentration of effervescent agents. The type and proportion of effervescent agents place an important role in effervescent release tablets.

After the stability studies there was no change in physical appearance and colour, formulations were analyzed for the period of three months for general tablet properties like weight, drug content, and disintegration and dissolution studies. Tablets are shown much deviation, it reveals that there was no significant change optimized tablets from initial to stability batches and it was found to be stable. Thus formulation of Deferasirox Efferent tablets helped to release the drug immediately and increases the flexibility of dosage for

BIBLOGRAPHY

[1]. Raymond C Rowe, Paul J Sheskey and Marian E Quinn, "Microcrystalline cellulose", Handbook of pharmaceutical excipients, 6th edition, 2009; 129-133.
[2]. Raymond C Rowe, Paul J Sheskey and Marian E Quinn, Handbook of pharmaceutical excipients 2009; 6th edition: 208-209.
[3]. Raymond C Rowe, Paul J Sheskey and Marian E Quinn, "Magnesium stearate", Handbook of pharmaceutical excipients, 6th edition, 2009;186.
[4]. Determination of calibration curve, Indian Pharmacopoeia, Ministry of health and Family Welfare, Govt. Of India, the Controller of Publications, Delhi, 1996; 2,144-145.
[5]. Lechman L., Liberman H.A., Kanig J.L., In., "Thickness test", The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing house, Bombay, 1987;300.
[6]. "Weight variation test", IP, Indian PHARMACOPOEIA, 1996; 2 (8.15), A-99.

[7]. Lechman L., Liberman H.A., Kanig J.L., In., "Determination of hardness", The Theory and Practice of Industrial Pharmacy , 3rd edition , Varghese Publishing House, Bombay , 1987;297.
[8]. Theoryand Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing House, Lechman L., Liberman H.A., Kanig J.L., In., "Friability test", The Theory Bombay, 1987;249.
[9]. Costa,P., Lobo,J.M.S "Modeling and composition of dissolution profile" Eur .J.Pharm Sci., 2001;13,123-133.