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FORMULATION DEVELOPMENT AND EVALUATION OF DEFERASIROX DISPERSIBLE TABLETS

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Abstract:
The main objective of this work was designed to Formulate and evaluate the Deferasirox Dispersible tablets. Model drug was characterized for Particle size distribution, bulk density and tapped density. The physical characterization reveals that API has very poor flow.Indicating that suitable granulation technology required for designing the dosage form.
Model drug is related to BCS class II drug (low solubility and high permeability), to increase the solubility of model drug, need to incorporate solubility enhancers like surfactants. The excipients selected for final formulation were compatible with model drug. The finalized formula was optimized and the final composition contains the following excipients like Microcrystalline cellulose, Lactose mono hydrate, Cremophore, Povidone, Silicon dioxide, Crospovidone and Magnesium Stearate. The finalized formulation F19 had comparable dissolution profile to reference product. Finalized formulation F19 was stable when stored at 40 °C/ 75% RH for 1M, 2M and 3M min HDPE container.
Key Words: *Deferasirox, Dispersible tablets, BCS class II drug, Dissolution profile.*

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1. INTRODUCTION:

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 [1-4].

Iron overload [5]

Iron overload is the result of many disorders and can lead to the development of organ damage with increased mortality. In humans total body iron concentration is maintained within the range of 200-1500 mg by inadequate adjustment of intestinal absorption, since no excretory mechanisms exist. In normal individuals, feed back mechanisms inhibit iron absorption as storage 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 whether it results from a primary defect in the regulation of iron balance or is secondary to other genetic or acquired disorders. A known example of primary iron overload is hereditary hemochromatosis (HHC), in which iron is absorbed in excess because of increased iron transfer from the enteral cells to the blood. The secondary includes iron overload either due to, or associated with, ineffective erythropoiesis, chronic liver diseases, parenteral administration or ingestion of excessive amounts of iron. Thalassemia major and sideroblastic anemia are the two best examples of iron overload secondary to blood transfusions and ineffective erythropoiesis [6-8].

Treatment of iron overload

The aim of treatment of iron storage disease is to remove from the body the excess iron that has accumulated. This can be done by employing iron chelators [8-10].

Table -1: Available Iron-Chelating Agents Used for the Treatment of Iron Overload

Agent	Brandname (Manufacturer)	Pharmacology	Route of Administration
Deferasirox	Exjade (Novartis)	Tridendate molecule; 2:1 stoichiometry for iron	Oral
Deferiprone	Ferriprox (Apotex)	Bidentate molecule; 3:1 stoichiometry for iron	Oral
Deferoxamine	Desferal (Novartis)	Hexadentate molecule; 1:1 stoichiometry for iron	IV

Oral solid dosage forms [11]

Drugs can be administered through different routes; however, of all the routes of administration, oral route of administration is most convenient for administering drugs for systemic effect because of ease of administration by manufacturing and dosage adjustments.

Tablets [12-15]

Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration].

Dispersible Tablets [16-18]

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.

2. MATERILAS AND METHODS:

2.1. MATERIALS USED

Deferasirox, Povidone (PVP K-30), Cremophore, Tween-80, Sodium lauryl sulphate, Microcrystalline cellulose, Lactose monohydrate, Colloidal silicon

dioxide, Crospovidone, Sodium Starch Glycolate (SSG), Ac-di-sol, Magnesium Stearate.

2.2. METHODS USED

FORMULATION DEVELOPMENT OF DEFERASIROX DISPERSIBLE TABLETS

Development Strategy:

Following ingredients and technology selected for formulation development of model drug based on the literature search and Preformulation studies. Model drug have poor flow properties which indicating suitable granulation technology to be used for the manufacture the product [14-16].

Formulation Design:

Wet granulation is the most widely used technique for granulation in the pharmaceutical industry. It involves granulate the powder with addition of a liquid solution (with or without binder). The wet mass subject to dry and then sized to obtain predetermined uniform sized granules. The liquid added binds the moist powder particles by different mechanisms in the wet state. More permanent bonds are formed during subsequent drying which leads to the formation of granules[17].

The development trials were started with wet granulation method in two parts. Part 1 includes. Formula optimization and part 2 include process optimization.

In formula optimization following selection and optimization trials was taken [17-19]

1. Optimization of Suitable diluents in intra granular part
2. Optimization of Suitable diluents in extra granular part
3. Selection and optimization of disintegrant
4. Selection and optimization of surfactant

In Process optimization following trial was taken:

5. Hardness optimization

3. RESULTS:

Table -2: Composition of formulations of model drug with different intra granular diluents

Ingredients	T-1	T-2	T-3	T-4
API	500	500	500	500
Micro crystalline cellulose(Avicel pH 101)	-	**350**	**175**	**150**
Lactose mono hydrate (Pharmatose 200)	**350**	-	**175**	**200**
Cremophore RH 40	51	51	51	51
Povidone k30	42.5	42.5	42.5	42.5
Silicon di oxide	12	12	12	12
Purified water	Qs	Qs	Qs	Qs

Table -3: Composition of formulations with different extra granular diluents

Ingredients (mg/tablet)	**F-1**	**F-2**	**F-3**	**F-4**
Intragranular				
API	500	500	500	500
Micro crystalline cellulose	150	150	150	150
Lactose mono hydrate	200	200	200	200
Cremophore RH 40	51	51	51	51
Povidone k30	42.5	42.5	42.5	42.5
Silicon di oxide	12	12	12	12
Purified water	Qs	Qs	Qs	Qs
Extragranular				
Micro crystalline cellulose	-	**321.25**	**385.5**	**514**
Lactose mono hydrate	**642.5**	**321.25**	**257**	**128.5**
Croscarmellose sodium	85	85	85	85
Magnesium Stearate	17	17	17	17
Total weight	1700	1700	1700	1700

Table -4: Composition of formulations with different disintegrants

Ingredients (mg/tablet)	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**	**F-10**	**F-11**	**F-12**	**F-13**	**F-14**	**F-15**	**F-16**
Intragranular												
API	500	500	500	500	500	500	500	500	500	500	500	500
MCC	150	150	150	150	150	150	150	150	150	150	150	150
Lactose	200	200	200	200	200	200	200	200	200	200	200	200
Cremophore RH 40	51	51	51	51	51	51	51	51	51	51	51	51
PVP K30	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5
Aerosil	12	12	12	12	12	12	12	12	12	12	12	12
P. water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Extragranular												
MCC	514	514	514	486.8	486.8	486.8	446	446	446	378	378	378
Lactose	128.5	128.5	128.5	121.7	121.7	121.7	111.5	111.5	111.5	94.5	94.5	94.5
Ac-di-sol	**85**	**-**	**-**	**119**	**-**	**-**	**170**	**-**	**-**	**255**	**-**	**-**
SSG	**-**	**85**	**-**	**-**	**119**	**-**	**-**	**170**	**-**	**-**	**255**	**-**
Crospovidone	**-**	**-**	**85**	**-**	**-**	**119**	**-**	**-**	**170**	**-**	**-**	**255**
Mag. Stearate	17	17	17	17	17	17	17	17	17	17	17	17
Total weight	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**

Table -5: Composition of formulations with different wetting agents

Ingredients (mg/tablet)	**F-17**	**F-18**	**F-19**	**F-20**	**F-21**	**F-22**	**F-23**	**F-24**	**F-25**
Intragranular									
API	500	500	500	500	500	500	500	500	500
MCC	150	150	150	150	150	150	150	150	150
Lactose	234	217	200	234	217	200	234	217	200
Cremophore	**17**	**34**	**51**	**-**	**-**	**-**	**-**	**-**	**-**
Tween 80	**-**	**-**	**-**	**17**	**34**	**51**	**-**	**-**	**-**
SLS	**-**	**-**	**-**	**-**	**-**	**-**	**17**	**34**	**51**
PVP k30	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5
Aerosil	12	12	12	12	12	12	12	12	12
P. water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Extragranular									
MCC	446	446	446	446	446	446	446	446	446
Lactose	111.5	111.5	111.5	111.5	111.5	111.5	111.5	111.5	111.5
Crospovidone	170	170	170	170	170	170	170	170	170
Mag. Stearate	17	17	17	17	17	17	17	17	17
Total weight	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**	**1700**

Table -6: Composition of optimized formulation

Ingredients (mg/tablet)	**F-19**
Intragranular	
API	500
MCC	150
Lactose	200
Cremophore RH 40	51
PVP k30	42.5
Aerosil	12
P. water	Qs
Extragranular	
MCC	446
Lactose	111.5
Crospovidone	170
Mag. Stearate	17
Total weight	1700

Table -7: Physical Parameters of Dried Granules

Flow property	**T-1**	**T-2**	**T-3**	**T-4**
Bulk density (gm/ml)	Lump formation observed	0.43	0.43	0.48
Tapped density (gm/ml)		0.61	0.58	0.57
Compressibility index		29.5	25.8	15.78
Hausner ratio		1.42	1.35	1.18
Flow of granules		Poor	poor	Good

Table -8: Physical Parameters of final blend

Formulation Code	**Tapped Density (gm/cm^3)**	**bulk density (gm/cm^3)**	**Compressibility Index (CI) (%)**	**Hausner ratio (HR)**	**Angle of repose (θ) degrees**
F1	0.588	0.526	10.526	1.12	25.12
F2	0.567	0.445	21.428	1.27	32.31
F3	0.559	0.457	18.18	1.22	31.35
F4	0.526	0.437	16.920	1.21	30.34

Table -9: Post compression parameters

Formulation code	**Weight variation (mg)**	**Hardness (KP)**	**Thickness (mm)**	**%Friability**	**D.T. (sec)**	**Dispersion time (sec)**
F1	1695±0.8%	8-9	5.81±0.05	1.15	260±5	285
F2	1702±0.5%	9-10	5.51±0.03	0.827	315±6	350
F3	1698±0.4%	11-12	5.43±0.02	0.260	405±4	445
F4	1697±0.4%	11-12	5.37±0.02	0.195	390±3	420

Table -10: Physical Parameters of final blends of formulation F5-F16

Formulation Code	Tapped Density (gm/cm^3)	Bulk density (gm/cm^3)	Compressibility Index (CI) (%)	Hausner ratio (HR)	Angle of repose (θ) degrees
F5	0.526	0.437	16.920	1.21	30.34
F6	0.500	0.416	16.667	1.20	29.76
F7	0.555	0.434	21.80	1.28	35.23
F8	0.571	0.420	25.0	1.33	36.35
F9	0.506	0.440	13.04	1.15	26.59
F10	0.548	0.453	17.39	1.21	30.34
F11	0.555	0.434	21.74	1.28	34.25
F12	0.548	0.442	19.34	1.24	30.32
F13	0.552	0.454	17.75	1.22	31.2
F14	0.569	0.464	18.52	1.23	32.21
F15	0.548	0.453	17.39	1.21	30.34
F16	0.454	0.372	18.06	1.22	26.57

Table-11-: Post compression parameters of formulation F5-F16

Formulation code	Weight variation (mg)	Hardness (KP)	Thickness (mm)	%Friability	D.T. (sec)	Dispersion time (sec)
F5	1697±0.5%	12-13	5.37±0.02	0.195	390±3	420
F6	1702±0.4 %	12-13	5.52±0.03	0.225	405±4	435
F7	1702±0.4%	12-13	5.71±0.03	0.305	250±3	280
F8	1701±0. 5%	12-13	5.54±0.02	0.125	325±3	350
F9	1702±0. 4%	12-13	5.63±0.02	0.108	350±2	380
F10	1696±0. 5%	12-13	5.90±0.03	0.260	210±3	220
F11	1695±0. 5%	12-13	5.44±0.02	0.195	230±4	245
F12	1698±0.4%	12-13	5.54±0.02	0.193	285±3	305
F13	1702±0.8%	12-13	5.90±0.03	0.293	125±4	140
F14	1703±0. 5%	12-13	5.45±0.02	0.380	200±3	225
F15	1701±0. 4%	12-13	5.49±0.02	0.178	235±3	260
F16	1701±0. 3%	12-13	5.73±0.02	0.183	120±3	140

Table 12: Physical Parameters of final blends of formulation F17- F25

Formulation Code	Tapped Density (gm/cm^3)	bulk density (gm/cm^3)	Compressibility Index (CI) (%)	Hausner ratio (HR)	Angle of repose (θ) degrees
F17	0.569	0.468	17.54	1.21	31.26
F18	0.506	0.422	16.61	1.20	33.57
F19	0.461	0.372	19.30	1.24	35.62
F20	0.57	0.47	17.54	1.21	30.34
F21	0.559	0.457	18.18	1.22	31.2
F22	0.567	0.459	19.93	1.25	33.52
F23	0.625	0.526	15.84	1.18	30.21
F24	0.61	0.526	14.81	1.17	28.52
F25	0.57	0.47	17.54	1.21	30.34

Table 13: Post compression parameters of formulation F17-F25

Formulation code	Weight variation (mg)	Hardness (KP)	Thickness (mm)	%Friability	D.T. (sec)	Dispersion time (sec)
F17	1701±0.3%	12-13	5.41±0.02	0.108	80±3	95
F18	1702±0.4%	12-13	5.53±0.03	0.178	100±2	120
F19	1701±0.3%	12-13	5.53±0.02	0.180	125±2	140
F20	1701±0.3%	12-13	5.33±0.03	0.332	105±5	110
F21	1702±0.4%	12-13	5.34±0.03	0.642	115±5	125
F22	1698±0.6%	10-11	5.38±0.02	0.635	120±2	135
F23	1699±0.4%	12-13	5.77±0.01	0.108	100±3	105
F24	1703±0.3	12-13	5.73±0.03	0.193	105±3	125
F25	1704±0.4%	12-13	5.72±0.02	0.382	120±2	130

Table 14: *Invitro* drug release profile of formulation F17-F19

Time (Minutes)	%Cumulative Drug Release			
	F 17	**F18**	**F19**	**Reference product**
10	62.3 ± 1.3	65.3 ± 1.8	83.2 ± 1.95	89.1 ± 1.34
20	74.5 ± 2.1	77.5 ± 1.9	92.7 ± 1.68	91.3 ± 1.32
30	77.4 ± 2.5	83.2 ± 2.2	94.9 ± 1.35	95.7 ± 1.25
45	80.0 ± 2.8	84.3 ± 2.3	96.3 ± 1.54	96.4 ± 1.34
60	82.7 ± 2.1	86.9 ± 2.5	97.4 ± 1.62	97.8 ± 1.12
%Assay	100.2	99.89	99.86	100.5

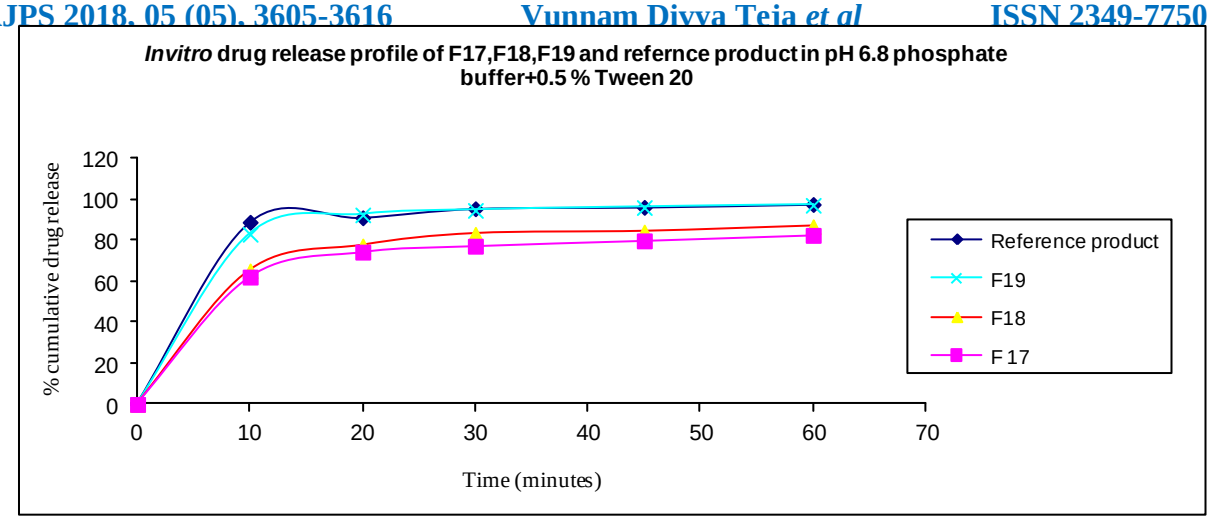

Fig 1: Comparison of *invitro* drug release profile of F17, F18, F19 and reference product

Table 15: Invitro drug release profile of formulation F20-F22

Time (Minutes)	%Cumulative Drug Release			
	F20	F21	F22	Reference product
10	65.0 ± 1.8	69.3 ± 1.6	83.2 ± 2.3	89.1 ± 1.34
20	77.2 ± 2.5	78.9 ± 1.5	89.0 ± 2.5	91.3 ± 1.32
30	78.7 ± 2.8	83.7 ± 2.1	88.7 ± 2.4	95.7 ± 1.25
45	81.3 ± 2.9	84.2 ± 2.3	90.4 ± 3.2	96.4 ± 1.34
60	84.1 ± 2.2	85.5 ± 2.7	91.0 ± 2.1	97.8 ± 1.12
%Assay	99.94	101.3	100.5	100.5

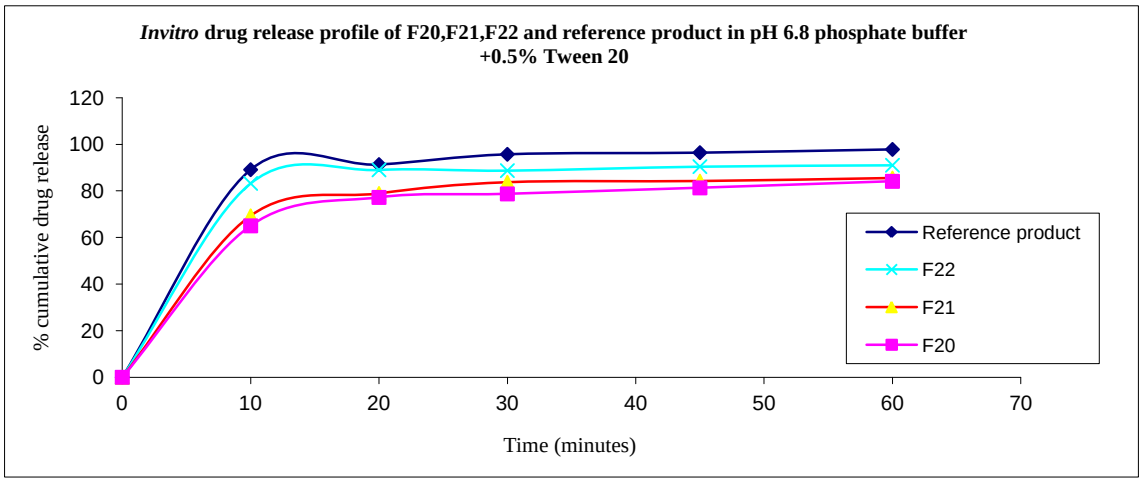

Fig 2: Comparison of *invitro* drug release profile of F20, F21, F22 and reference product

Table 16: *Invitro* drug release profile of formulation F23-F25

Time (minutes)	%Cumulative Drug Release			
	F23	F24	F25	Reference product
10	63.7 ± 2.2	68.5 ± 2.3	72.17 ± 2.1	89.1 ± 1.34
20	76.6 ± 2.0	78.5 ± 2.5	81.7 ± 2.3	91.3 ± 1.32
30	78.5 ± 2.0	81.2 ± 2.1	87.2 ± 2.7	95.7 ± 1.25
45	81.4 ± 2.1	83.1 ± 1.6	91.3 ± 2.4	96.4 ± 1.34
60	84.5 ± 1.8	85.1 ± 1.8	92.5 ± 1.8	97.8 ± 1.12
%Assay	99.92	100.2	101.3	100.5

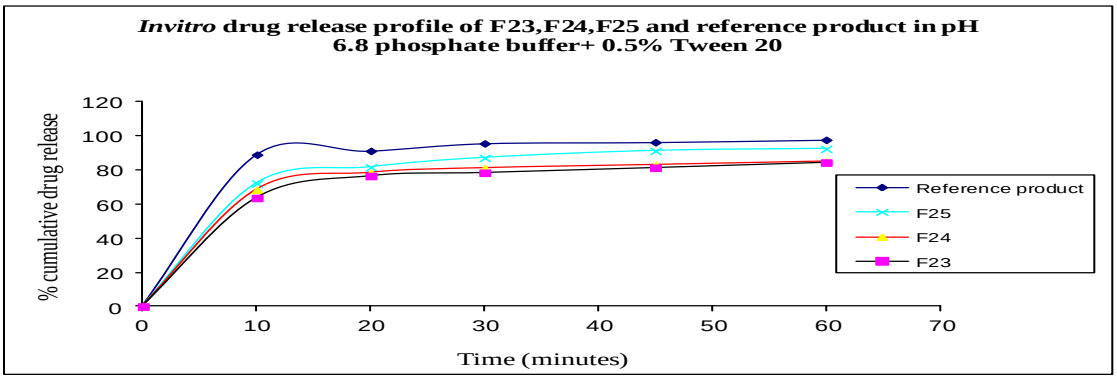

Fig 3: Comparison of *invitro* drug release profile of F23, F24, F25 and reference product

Table 17: *Invitro* drug release profile of formulation F19, F22, F25

Time (minutes)	%Cumulative Drug Release			
	F19	F22	F25	Reference product
10	83.2 ± 1.95	83.2 ± 2.3	72.17 ± 2.1	89.1 ± 1.34
20	92.7 ± 1.68	89.0 ± 2.5	81.7 ± 2.3	91.3 ± 1.32
30	94.9 ± 1.35	88.7 ± 2.4	87.2 ± 2.7	95.7 ± 1.25
45	96.3 ± 1.54	90.4 ± 3.2	91.3 ± 2.4	96.4 ± 1.34
60	97.4 ± 1.62	91.0 ± 2.1	92.5 ± 1.8	97.8 ± 1.12
%Assay	99.86	100.5	101.3	100.5

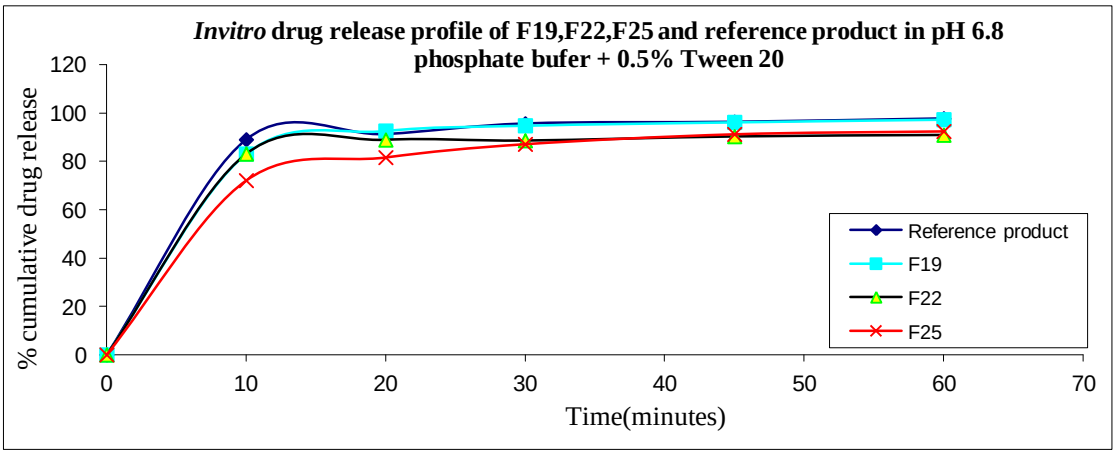

Fig 4: Comparison of *invitro* drug release profile of F19, F22, F25 and reference product

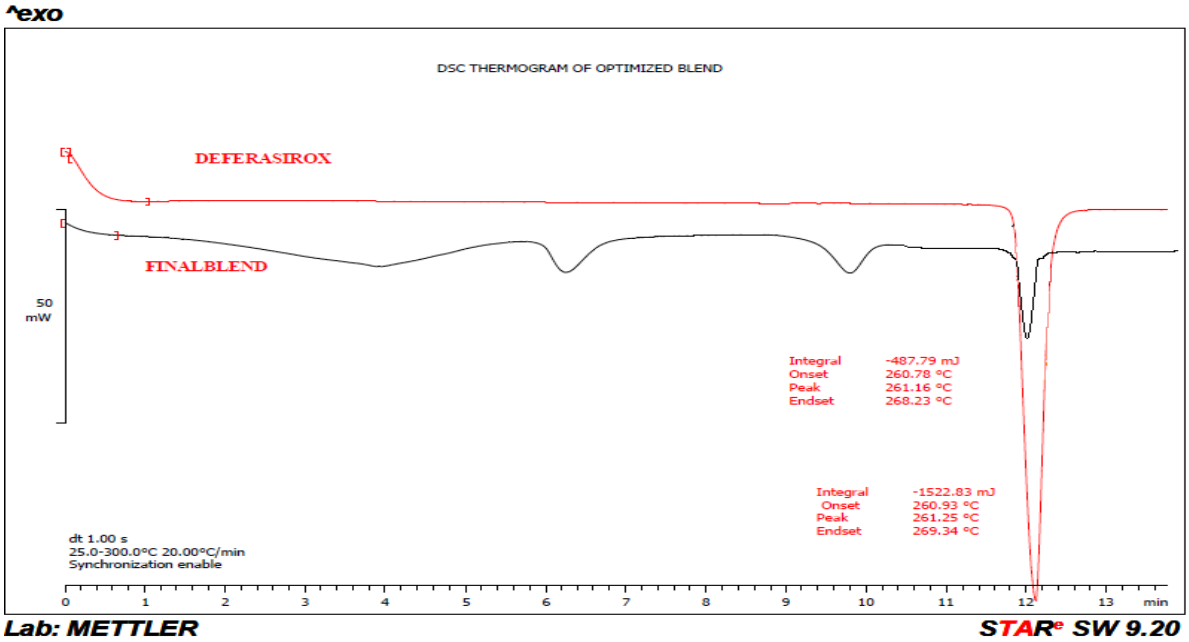

Fig 5: DSC Thermogram of Model Drug, Final blend

Table 18: Physical parameters of dispersible tablets (F19) initial, 1M, 2M and 3M stability at 40±2 °C/ 75±5 %RH

Parameter	Initial	1 Month	2 Month	3 Month
Description	White	White	White	White
Avg. wt (mg)	1701±0.5%	1702±0.5%	1702±0.5%	1702±0.6%
Hardness (KP)	12-13	12-13	12-13	12-13
Thickness (mm)	5.72±0.02	5.74±0.02	5.74±0.03	5.75±0.03
Friability (%)	0.183	0..190	0.192	0.215
Disintegration time (sec)	120±4	120±2	125±4	125±5
Dispersion time (sec)	140	140	150	150

Table 19 : *Invitro* drug release data of dispersible tablets (F19) initial, after 1M, 2M and 3M stability at 40±2 °C / 75±5 %RH.

Time interval (min)	% Cumulative drug release				
	Initial	1 Month	2 Month	3 Month	Reference Product
10	83.2±1.6	83.3±1.7	82.6±1.9	80.6±1.5	89.1 ± 1.34
20	92.7±1.1	92.0±1.5	91.8±1.5	90.6±1.7	91.3 ± 1.32
30	94.9±1.7	96.2±1.6	94.4±2.1	92.5±2.3	95.7 ± 1.25
45	96.3±1.9	95.9±2.1	95.7±1.8	94.1±1.6	96.4 ± 1.34
60	97.4±2.3	97.1±1.2	96.8±1.9	95.6±1.4	97.8 ± 1.12
%Assay	99.86	100.5	99.57	98.82	100.5

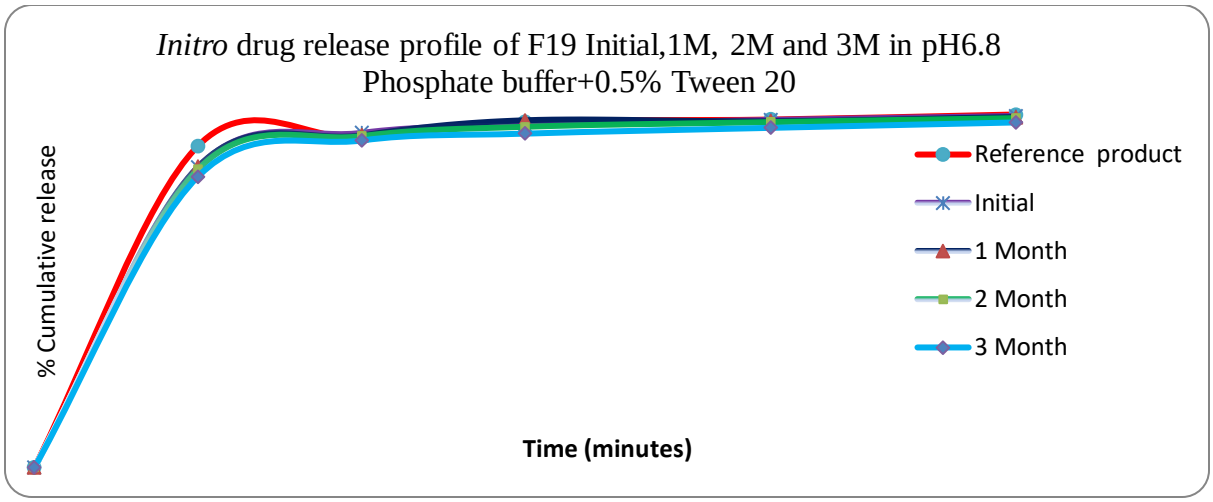

Fig 6 : *Invitro* drug release data of dispersible tablets (F19) initial, after 1M, 2M and 3M stability at 40±2 °C / 75±5 %RH.

4. CONCLUSION:

Model drug was characterized for Particle size distribution, bulk density and tapped density. The physical characterization reveals that API has very poor flow. Indicating that suitable granulation technology required for designing the dosage form. Model drug is related to BCS class II drug (low solubility and high permeability), to increase the solubility of model drug, need to incorporate solubility enhancers like surfactants. The excipients selected for final formulation were compatible with model drug. The finalized formula was optimized and the final composition contains the following excipients: Microcrystalline cellulose, Lactose mono hydrate, Cremophore, Povidone, Silicon dioxide, Crospovidone and Magnesium Stearate .The finalized formulation had comparable dissolution profile to reference product. Finalized formulation was stable when stored at 40 °C/ 75% RH for 1M, 2M and 3M min HDPE container. Formulation 19 was found to be satisfactory when compared to other formulations. The disintegration time, dispersion time was found to be satisfactory and percentage of drug release matches with the reference product. So, the batch size was increased in further trial to check the reproducibility.

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