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DESIGN AND CHARACTERIZATION OF DISPERSIBLE TABLET OF FEXOFENADINE HCl

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ABSTRACT

The objective of the work was to Design and evaluate the Dispersible drug delivery system containing Fexofenadine HCl (FEX) as a model drug. FEX tablets were prepared by direct compression and wet granulation method incorporating Crospovidone, cross caramellose sodium, Doshion-Ds, Doshion-D as disintegrants. MCC and lactose were used as diluents, magnesium stearate and talc used as lubricant and glidant. Aspartame as sweetening agent, vanilla as flavoring agent, Erythrosine supra as coloring agent, Aerosil, Pregelatinised starch as suspending and binding agent respectively. Dissolution profiles were studied in 0.1N HCl medium. Tablets were also evaluated for standards of dispersible tablets and were compared with marketed products. The optimized formulation was checked for stability at 30ºC, 65% RH and 40ºC, 75% RH which was found to be stable. The drug release profile of the both formulations was well released within 30 minutes and uniform drug release as compared with marketed formulation.

KEYWORDS: Fexofenadine **(**FEX), Disintegrants, Drug release, Dissolution profile.

INTRODUCTION[1-7]

Dispersible tablets are uncoated or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion.

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. The different dosage forms include tablets and capsules. Nearly 35% of the general population, especially the elderly patients and children suffer from Dysphagia or difficulty in swallowing, which results in high incidence of noncompliance and ineffective therapy. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, developmentally disabled, non co-operative patients and patients with reduced liquid intake plans or patients suffering from nausea. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing and due to lack of water. To overcome these problems, formulators have considerably dedicated their effort to develop a novel type of tablet dosage form for oral administration, i.e., one, which disintegrates within three minutes.

IDEAL DISPERSIBLE DOSAGE FORM OFFERS

- ✓ High drug loading.
- ✓ Ability to provide advantages of liquid medication in the form of solid preparation
- ✓ Adaptable and amenable to existing processing and packaging machinery.
- ✓ Cost- effective.
- ✓ Dispersible tablets are a perfect fit for pediatric & geriatric patients.
- ✓ Improved patient compliance.
- ✓ Rapid onset of action and may offer an improved bioavailability.
- ✓ Patients having difficulty in swallowing tablet can be easily administered using this type of dosage form.
- ✓ Gives accurate dosing as compared to liquids.
- ✓ Good chemical stability.

Dispersible tablets combine benefits of liquid dosage forms with a solid dosage forms and are preferred for pediatric and geriatric patients. The drug from conventional dispersible tablets has tendency to settle at the bottom or adhere to the sides of the containers upon dispersion in

water, leading to incomplete dosage.

The aim of present work to develop a dispersible dosage which upon dispersion in water forms a homogenous dispersion with reduced sedimentation rate, thus ensuring uniformity of dosage.

ADVANTAGES OF DISPERSIBLE TABLES

- ✓ They are lightest and most compact of all oral dosage form.
- ✓ Disintegration is faster than the regular compact tablets that are disintegration is seen within few seconds to 3 minutes.
- ✓ Due to quicker disintegration, the e uniformity of dispersion is seen, and the dissolution profile is also faster than usual compressed tablets.
- ✓ Dispersible tablets produce greatest ease if swallowing. The formal is taken orally in the form of uniform dispersion or suspension.
- ✓ Dispersible tablets replace the use of conventional type dry syrupdosage forms due to reduction in cost, inventoryk, improved palatability and stability after reconstitution.
- ✓ Dispersible tablets are formulated with an objective of improving the dissolution of poorly soluble drugs by using various superdisintegrants available.
- ✓ Dispersible tablets are easy and convenient to handle during transport. No risk of breakage of the packing material.
- ✓ Dispersible tablets can easily administer to pediatric and geriatric patients.
- ✓ They are well suited for large scale production.
- ✓ They can provide both elegance and mouth feel.

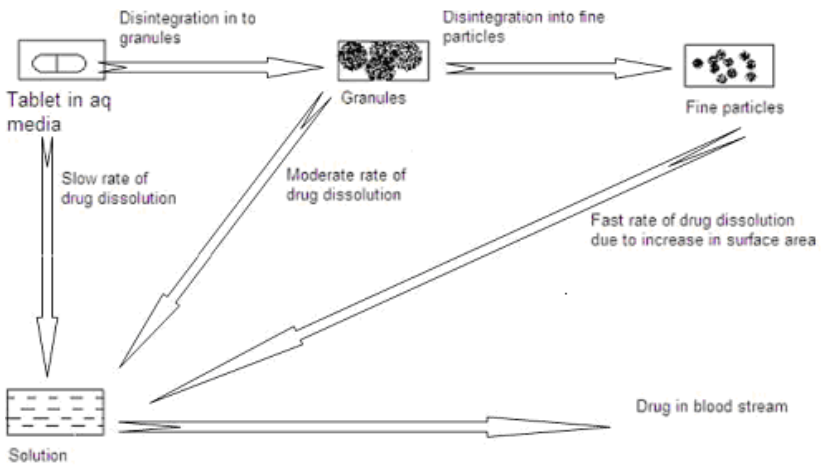

Figure No 1: Schematic Representation of Tablet disintegration and subsequent drug dissolution

MATERIALS AND METHODS

Following Ingredients used to Develop Dispersible Tablet of Fexofenadine HCl which is kindly supplied by KAPL Bangalore, India. Distilled water, Ethanol and other solvents were purchased from local suppliers. All the chemicals were used as supplied, without further purification.

Table 1. Descriptions and Composition of the Formulation

SL.NO	INGREDIENTS	USED AS
1	Fexofenadine hydrochloride	Active ingredient
2	Cross caramellose sodium	Disintegrant
3	Cross povidone	Disintegrant
4	Doshion - P-544 Ds	Disintegrant
5	Doshion- P-544 D	Disintegrant
6	Aerosil	Suspending agent
7	Aspartame	sweetener
8	vanilla	Flavoring agent
9	Magnesium stearate	lubricant
10	Talc	Glident
11	Microcrystalline cellulose	Diluent
12	lactose	Diluent

FORMULATION OF DISPERSIBLE TABLETS OF FEXOFENADINE HCl BY DIRECT COMPRESSION AND WET GRANULATION METHODS:

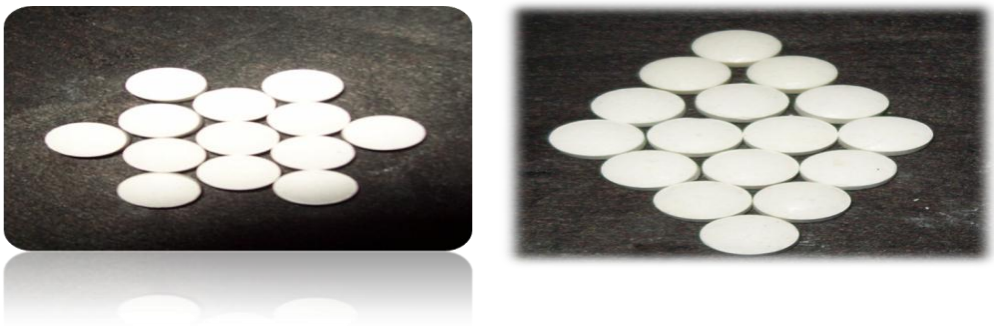

Figure 2. Dispersible tablets of Fexofenadine Hcl

All the ingredients were passed through # 60 meshes separately. The drug and the diluents were mixed in small portion of both each time and blending it to get uniform mixture and set aside. The other ingredients were weighed and mixed in geometrical order. Flavoring agents followed by lubricants was added at the end and mixed thoroughly. The blend was compressed using 8 mm standard concave punch size to get a tablet weight of 200 mg using 16 – station rotary machine; Elit Jemkay Pvt Ltd, Ahmedabad.

EVALUATION OF PRE-COMPRESSION PARAMETERS

1. Bulk density (D_b)[8]

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by

$$D_b = M / V_0$$

Where, M is the mass of powder.

V_0 is the bulk volume of the powder.

2. Tapped density (D_t)[9]

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by,

$$D_t = M / V_t$$

Where, M is the mass of powder.

V_t is the tapped volume of the powder.

3. Angle of repose (θ)[10]

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height ‘h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation,

$$\theta = \mathbf{Tan^{-1}\ (h/r)}$$

Where θ =Angle of repose**,** h=Height of pile**,** r=Radius of the base of the pile.

Table 2. Angle of repose and type of flow

Angle of repose	Type of flow
<25	excellent
25-30	good
30-40	passable
>40	Very poor

4. Carr's Consolidation Index (I)[11]

Carr's index is an indication of the compressibility of a powder. It is expressed in percentage and is given by

$$I = D_t - D_b / D_t \times 100$$

Where Dt =Tapped density, D_b=Bulk density

Table 3. Relation between Carr's index (I) of a powder and its flow characteristics

Carr's index (%)	Type of flow
5-15	Excellent
12-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very Poor
>	Extremely Poor

5. Hausner's ratio[12]

It is the ratio of the tapped density to the untapped density. It is given by

$$H = Dt/Db$$

POST COMPRESSION PARAMETERS

1. General Appearance:

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Tablet size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

2. Hardness[13]

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in Kg / cm^2.

3. Friability (F)[14]

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage **(%)**. 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator.

The friabilator was operated at 25 rpm for four minutes. The tablets were weighed again (W_{final}). The percentage friability was then calculated by:

$$F = \frac{(W_{initial}) - (W_{final})}{(I_{nitial})} \quad X\ 100$$

4. Weight Variation[15]

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighting upto 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

$PD = (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100$

Where PD= Percentage deviation, W_{avg} =Average weight of tablet, $W_{initial}$ =Individual weight of tablet.

5. Thickness[16]

The thickness of the tablets was measured by screw gauge. It is expressed in mm.

6. Disintegration Time[17]

Tablets comply with the test for disintegration of tablets use *water as* the liquid at $15C^0$ to $25C^0$. Add a disc to each tube. Operate the apparatus for 15 min, unless otherwise justified and authorized, and examine the state of the tablets. If the tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated. Dispersible tablets disintegrate within 3 minutes.

7. Wetting Time

A piece of tissue paper folded twice was placed in a small Petri plate (internal diameter = 6.5 cm) containing 10ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

8. Fineness of dispersion[18]

Place 2 tablets in 100 ml of *water* and stir until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 mm.

9. Assay [19]

I stock solution: Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 100mg of Fexofenadine hydrochloride and transferred to a 100ml volumetric flask containing few ml of Acetonitrile and shake for some time and make up the volume up to 100ml with Acetonitrile.

II stock solution: Pipette out 5 ml from the I stock solution into another 100 ml volumetric flask and make up the volume with Acetonitrile (i.e.50 µg/ml).

Aliquots: From the above solution withdraw 1ml and 5 ml quantity (as per Beer's range 2.5-25 µg/ml) and the volume was made up to 10 ml with Acetonitrile.

The absorbance was measured at 220 nm and Acetonitrile using as blank.

The concentrations were calculated using the formula

Y = mx + C

The percentage of drug content was estimated.

10. In vitro Release studies: [20]

- Apparatus : USP type II Dissolution apparatus
- Dissolution medium : 0.1N HCl
- Temperature : 37± 0.5 ^{o} C
- RPM : 50
- Vol. withdrawn and replaced : 3 ml for every 5 min
- λ max : 220nm
- Blank solution : Acetonitrile
- Beer's range : 2.5-25 µg/ml

Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot.

Stability studies[21]

The samples are stored in air tight container to protect from light and humidity. A Study of stability of pharmaceutical product is essential. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Stability studies are important to prevent the economic

repercussions of marketing of an unstable product, since subsequent withdrawal and reformulation may lead to considerable financial loss. From the point of view of safety to patient, it is important that the patient receives a uniform dose of the drug throughout the shelf of the product.

METHOD

The formulation was stored at different storage conditions at elevated temperatures such as 35^0C,65 % RH and 40^0C,75% RH for 2 months .The samples were withdrawn at monthly intervals and checked for photo degradation, physical changes, disintegration time, drug content and *in vitro* drug release studies.

RESULT AND DISCUSSION

Evaluation Parameters

Pre compressional parameters - flow properties optimization wet granulation

Flow properties play an important role in pharmaceuticals especially in tablet formulation. The bulk density of the powder for trial batch and also for optimized formulation was in the range of 0.26 to 0.36 gm/cc, the tapped density was in the range of 0.31 to 0.36 gm/cc, which indicates powder, was not bulky. The angle of repose of the drug powder was in the range of 19.6 ^{0} to 26.9 ^{0}, which indicate good flow of the powder, the Carr's index was found to be in the excellent range of 9-14 indicating compressibility of the tablet blend is good.

Flow properties of wet granulation the bulk density of the granules 0.27-0.35 gm/cc, the tapped density was in the range of 0.34-0.44 gm/cc, the angle of repose of the drug powder was in the range of18 ^{0} to $20^{0,}$ which indicate good flow of the powder, the Carr's index was found to be in the excellent range of 16-19 indicating compressibility of the tablet blend is fairly passable good.

Post compressesional parameters

The weighed quantities of drug, disintegrants and excipients were mixed thoroughly using lactose and Mcc as diluent for uniform mixing. The mixed powder was subjected to direct compression using 8 mm standard concave punch and Pregelatinised starch, erythrosine supra, Aerosil as binder, coloring, suspending agent respectively. The compressed tablets were tested for physical parameters like hardness, weight variation, friability, thickness and evaluated for the drug content, *in- vitro* drug release, wetting time, dispersion time, disintegration time profiles and stability studies.

✓ **Weight variation**

Prepared tablets were evaluated for weight variation and percentage deviation from the average weight was found to be within the prescribed official limits.

✓ **Friability**

The friability of the formulations was found to be between 0.199 - 0.545% which was found to be within the official requirement (i.e. not more than 1%).

✓ **Tablet thickness and hardness**

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (8 mm) and the weight of the tablet (200mg). The thickness of the trial batch from F1-F6 was found to be 3.9-4 mm hardness was found to be 3.9-4.0 Kg/cm^2 and the thickness of the tablet of optimized formulation and wet granulation was found to be 3.8 mm and hardness was found to be 4 kg/cm^2 which have good mechanical strength. Same thickness and hardness remains same in wet granulation.

✓ **Drug content**

The drug content estimation data for all the formulations and optimized formulation were found to be within the limit (not less than 90% and not more than120%).

✓ **Drug release studies**

In- vitro dissolution studies were performed for all the formulations using USP type II tablet dissolution tester employing basket type at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. The samples withdrawn were analyzed by using UV spectrophotometer. Formulations F4, shown good drug release 90 ± 0.02% to 100 ± 0.03%when compared to others. Formulations F2 shown less drug release may be due to the presence of cross caramellose sod used alone in formulation where in remaining formulations disintegrants used in combination as mentioned above.

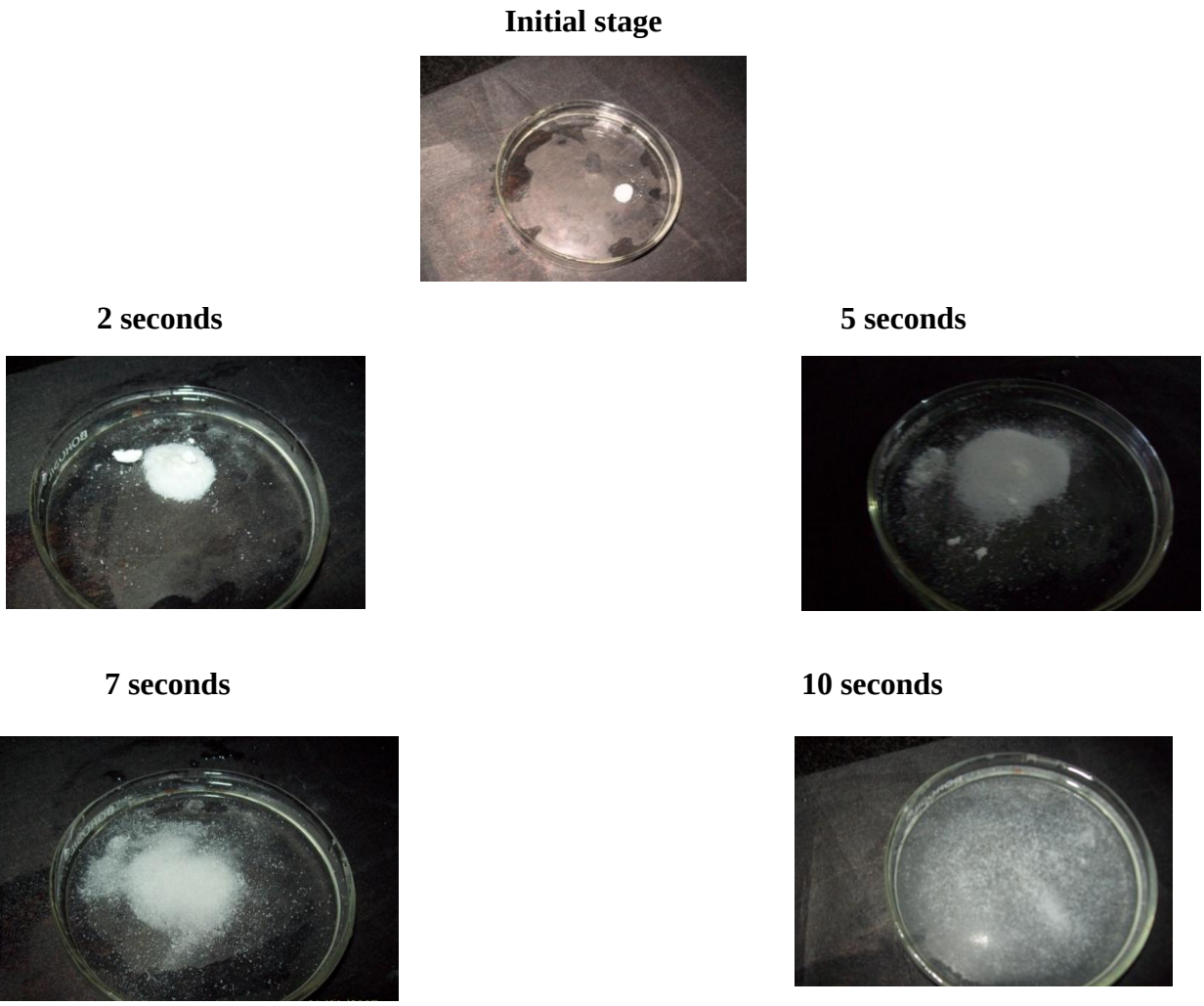

Figure 3 ***Diagrammatic Representation of In – Vitro Dispersion Time of Dispersible Tablets***

Table 4 ***Pre-compression parameters of dispersible tablets***

Formula	Parameters				
	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Angle of repose (˚)	Hausner's ratio
1	0.29 ± 0.00	0.34 ± 0.00	9.49 ± 0.49	21.15 ± 0.15	1.18 ±0.07
2	0.26 ± 0.00	0.36 ± 0.00	9.28 ± 0.19	21.15 ±0.15	1.16 ±0.06
3	0.27 ± 0.01	0.36 ± 0.01	19 ± 1.00	21.55 ±0.25	1.12 ± 0.12
4	0.28 ± 0.01	0.31 ± 0.01	19 ± 1.00	18.63 ±0.37	1.17 ± 0.07
5	0.33 ± 0.00	0.37 ± 0.01	9.47 ± 0.02	21.4 ± 0.40	1.16 ± 0.05
6	0.34 ± 0.01	0.40 ± 0.00	8.87 ± 0.02	19.67 ± 0.11	1.15 ± 0.15

*Each value represented as mean ± Standard Deviation of 3 observations

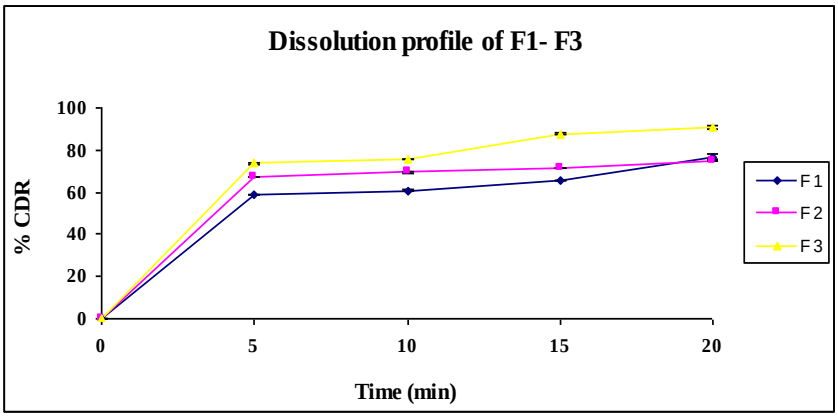

Figure 4 ***Dissolution profile for Dispersible tablet Formulations F1 – F3***

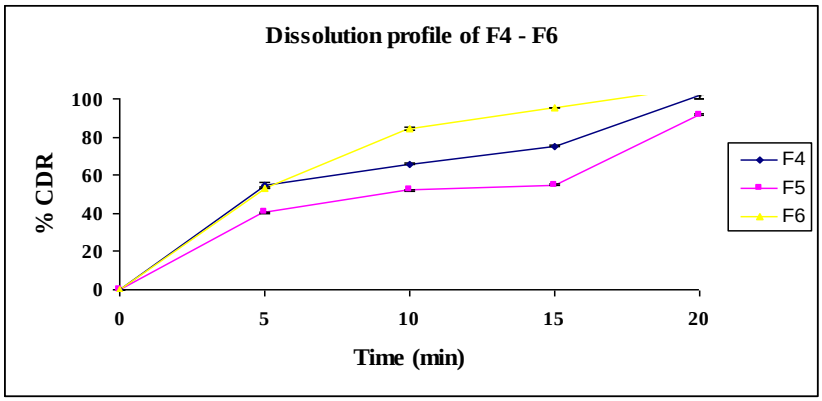

Figure 5 ***Dissolution profile for Dispersible tablet Formulations F4 – F6***

MARKETED PRODUCT

Fexofenadine Hydrochloride (Allegra ^{tm} 120 mg) AVENTIS

Table 5 ***Parameters of marketed product***

Parameters	Values
Weight variation	420 ± 0.03
Drug content	117.9 ± 0.01

*Each value represented as mean ± Standard Deviation of 3 observations

DISSOLUTION STUDIES OF MARKETED PRODUCT

Table No 6 ***Dissolution profile of marketed product***

Time in minutes	%CDR
10	46.86944
20	57.22355
30	70.34185
40	79.36175
50	83.73845

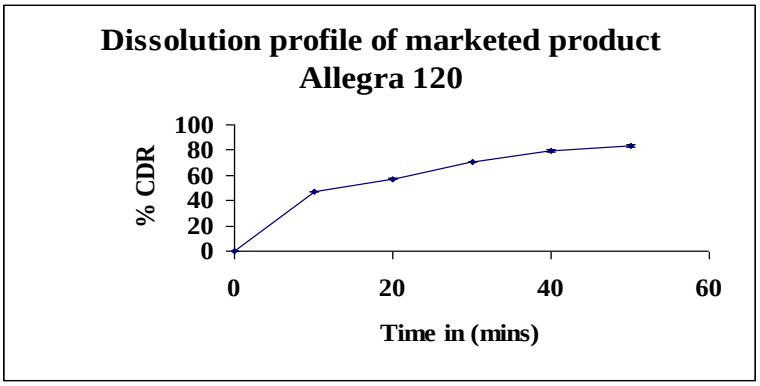

Figure 6. ***Dissolution profile of marketed product***

STABILITY STUDIES

The stability studies were performed on formulations such as optimized formulation and as well as wet granulation both were kept at conditions such as 30^0C,65% RH and 40^0C,75% RH and analyzed for physical appearance of the tablets, Disintegration time, drug content and *in -vitro* dissolution studies in 0.1N HCl. No significant difference was observed for above parameters and the optimized formulation as well as wet granulation showed good stability. Therefore the main objective of the study was achieved.

CONCLUSION

All the preformulation parameters viz, Carr's index, Hausner's ratio and Angle of repose values are within the acceptable range and hence the tablets comply with requirement. Post-compression parameters such as hardness, friability, weight variation, thickness measurement, disintegration time and drug content determination have indicated that the values are within the acceptable range. The drug release profile of the both formulations was well released within 30 minutes and uniform drug release as compared with marketed formulation. Overall, the results suggest that ODTs of Fexofenadine HCl containing co-processed superdisintegrating agent could be successfully formulated. Thus the present study has demonstrated the potential of ODTs of FEX for rapid absorption, leading to enhanced bioavailability, resulting in efficacious therapy and improved patient compliance.

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