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Original Article

FORMULATION, *IN VITRO*, AND *IN VIVO* EVALUATION OF TASTE-MASKED ORAL DISINTEGRATING TABLETS OF FEXOFENADINE HYDROCHLORIDE USING SEMISYNTHETIC AND NATURAL SUPERDISINTEGRANTS

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ABSTRACT

Objective: The aim of the present research work was to prepare and evaluate taste-masked oral disintegrating tablets (ODT) of Fexofenadine hydrochloride.

Methods: In the present work, Eudragit EPO, a taste masking agent and Karaya gum (GK) (natural), Sodium starch glycolate, and Croscarmellose sodium (CCS) (semi-synthetic) super disintegrants in three ratios (3, 6,9%) were used. Taste masked granules were prepared by different ratios of the drug: Eudragit EPO (1:1, 1:1.5, 1:2) by wet granulation method. The optimized taste-masked granules (1:2) were selected by sensory evaluation test to prepare 9 Fexofenadine ODT (FH1-FH9) formulations. These were evaluated for different parameters. Then desirability function (DF) was calculated for all formulations using disintegration time (DT), time taken for the tablet to release 90% of the drug ($t_{90\%}$), and % drug dissolved in 10 min (Q10) as significant parameters.

Results: The best formulation (FH6) showed the highest DF value due to less DT and 100% *in vitro* drug release within 15 min. Thus, FH6 formulation containing 9% CCS was selected as the best among the prepared formulations to which *in vivo* studies were performed on rabbits to find maximum plasma concentration (Cmax), time taken to reach maximum concentration (t_{max}), area under the curve (AUC), rate of elimination (Kel), absorption rate (Ka) and half-life($t_{1/2}$) and compared with Fexofenadine (Allegra) marketed tablets. Total bioavailability was increased for the test formulation compared to the reference formulation.

Conclusion: Fexofenadine was successfully prepared as ODT with increased AUC and decreased t_{max} to which stability studies were conducted which were found to be stable.

Keywords: Gum karaya, ODT, $t_{90\%}$, Q10, AUC, t_{max}

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INTRODUCTION

The most widely used dosage forms are tablets and capsules. But swallowing difficulty is a major drawback of these dosage forms. Oral disintegrating tablets (ODT) represent a rapidly emerging drug delivery system with better patient compliance and are very helpful for patients who have difficulty in swallowing [1-3]. As ODTs disintegrate in the oral cavity within a matter of few seconds, these are very much useful for patients who are suffering from dysphagia [4, 5].

These orally disintegrating tablets release the medicament in the mouth for absorption through local oromucosal tissue and through pre-gastric (oral cavity, pharynx, and esophagus), gastric (stomach) and post-gastric (small and large intestine) segments of the Gastro-Intestinal Tract. Oral disintegrating dosage forms are particularly suitable for patients who have difficulty swallowing traditional tablets with a glass of water.

ODT's will be beneficial for the patients who cannot swallow, inclusive of the aged, stroke victims, bedridden patients, patients with renal failure, and patients who refuse to swallow, which includes pediatric and amp; psychiatric patients. There is no need for water to swallow the dosage form that is a noticeably convenient characteristic for patients who are traveling. Fast dissolution and absorption of the drug from ODT will produce a fast onset of action. A few drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach. In such instances, the bioavailability of a drug is accelerated.

Pre gastric absorption can result in improved bioavailability and, due to decreased dose; enhance overall clinical performance through a reduction of undesirable outcomes. Because of the good mouthfeel property of ODT, it enables to change the perception of medication as bitter tablets, mainly in pediatric patients. The hazard of choking or suffocation at some point of oral delivery of conventional formulation because of physical obstruction is prevented, therefore offering stepped forward protection. A new business opportunity like product differentiation, product promotion, patent extensions, and life cycle control will be obtained.

ODT's are useful in cases that include movement sickness, unexpected episodes of allergic attack, or coughing, where extremely rapid action is required. An enhanced bioavailability will be there specifically in instances of insoluble and hydrophobic drugs because of the fast disintegration and dissolution of these tablets. These are stable for a longer duration of time since the drug remains in solid dosage form till it is consumed. So, it combines the benefit of a solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations while also offering advantages over both traditional dosage forms. It provides the convenience of a tablet formulation while also permitting the convenience of swallowing provided by a liquid formulation

Keeping in view of the above advantages of ODTs in the present work, Fexofenadine HCl and H1 histamine antagonist used in the treatment of allergies and urticaria, which require rapid action, were selected based on the criteria of bitter taste, low solubility, and low bioavailability to formulate into ODT.

Hence considering the fact that antihistamine drugs are used for the treatment of various indications, which require rapid onset of action, there is a great scope and need for developing a formulation of orally disintegrating tablets for rapid action, with enhanced patient compliance.

MATERIALS AND METHODS

Materials

Fexofenadine hydrochloride was obtained from Dr. Reddy's Laboratories Ltd; Hyd, Eudragit E 100 was obtained from Colorcon Asia PVT. Ltd, Goa. Sodium starch glycolate and Croscarmellose sodium were obtained from Universal lab Pvt. Ltd, Mumbai. Gum karaya was obtained from Spectrum Labs, Hyd. Aspartame and Mannitol were obtained from SD Fine Chemicals, Mumbai. All chemicals and reagents used in this study were of analytical grade.

Methods

Preparation of calibration curve

The standard stock solution of Fexofenadine was prepared by dissolving Fexofenadine hydrochloride in pH 6.8 phosphate buffer to make a concentration of 1000µg/ml. Different aliquots were taken from the stock solution and diluted with pH 6.8 phosphate buffer separately to prepare series of concentrations of 2, 4, 6, 8, 10, 12µg/ml. The absorbance of all samples was measured at 259 nm against pH 6.8 phosphate buffer as a blank after determining λmax by scanning drug solution in UV region of 200-400 nm. The calibration curve was prepared by plotting Concentration versus Absorbance of Fexofenadine.

Preparation of taste-masked granules—Wet granulation method

Drug and Eudragit E 100 were mixed in different ratios (1:1, 1:1.5, and 1:2) uniformly (TFH1, THF2, TFH3) as given in table 1 and the granules were prepared to employ the wet granulation method using starch paste as a binder. The granules were dried at 60 °C and the granules that passed through a 20-mesh sieve but remained on a 22-mesh sieve were used for the preparation of tablets [6].

Table 1: Ratios of drug and eudragit E 100 for taste masking

S. No.	Code	The ratio of drug and eudragit E 100
1	TFH1	1:1
2	TFH2	1:1.5
3	TFH3	1:2

Evaluation of taste

A sensory test on the taste of all granule preparations (TFH1, TFH2, and TFH3) was performed using a taste panel consisting of 6 healthy adult volunteers from whom informed consent was first obtained after approval of the Institutional Human Ethics Committee (IHEC/VIPS/005/2018). Before the study, the volunteers were briefed on the nature, purpose, duration, and risk of the study [7, 8]. They rinsed their mouths sufficiently before and after the tasting. The taste-masked granules (≈ 10 mg) of different ratios were kept in the volunteer's mouth for 30 sec and then spitted out. The taste score was calculated based on the bitter intensity scale, which was in the range of 0-4; '4' being very bitter, '3' bitter, '2' slightly bitter, '1' tasteless, and '0' for good taste. The volunteers were asked to rank accordingly based on the evaluation of given samples. Then total score and average score from 6 volunteers were calculated for each ratio of drug and Eudragit [9].

Formulation of taste-masked oral disintegrating tablets (ODTs)

Total nine oral disintegrating tablets (FH1-FH9) were prepared using different percentages (3, 6, 9%) of three super disintegrants, Sodium Starch Glycolate (SSG), croscarmellose sodium (CCS), and Gum Karaya (GK), with a composition as given in table 2. Accurately weighed optimized taste-masked granules equivalent to 30 mg of Fexofenadine were mixed with SSG/CCS/GK, mannitol, aspartame using a blender for about 10-15 min. Then, magnesium stearate and talc were added and mixed for a further 10 min and compressed into tablets of the weight of about 200 mg by direct compression method with flat punches [10].

Table 2: Composition of different formulations of taste-masked ODTs of fexofenadine hydrochloride

S. No.	Formulation code (mg)	Ingredients per tablet								
		FH1	FH2	FH3	FH4	FH5	FH6	FH7	FH8	FH9
1	TFH3 Granules (mg) (Best taste-masked granules containing Fexofenadine 30 mg)	90	90	90	90	90	90	90	90	90
2	Sodium starch Glycolate(mg)	6	12	18	-	-	-	-	-	-
3	Croscarmellose sodium(mg)	-	-	-	6	12	18	-	-	-
4	Gum karaya (mg)	-	-	-	-	-	-	6	12	18
5	Mannitol (mg)	92	86	80	92	86	80	92	86	80
6	Aspartame (mg)	2	2	2	2	2	2	2	2	2
7	Magnesium stearate(mg)	5	5	5	5	5	5	5	5	5
8	Talc(mg)	5	5	5	5	5	5	5	5	5
9	Total weight (mg)	200	200	200	200	200	200	200	200	200

Evaluation methods

Precompression parameters (flow properties)

The uniformly mixed powders of all formulations were evaluated for flow properties by determining the following parameters before compression [11-13].

The angle of repose (θ) was determined by the fixed funnel method using an equation,

$\theta = \tan - 1h/r$, Where θ is the angle of repose, h is the height of the pile of powder, r is the radius of the base of the pile. Apparent bulk density (D_b) was determined using bulk density apparatus by an equation, $Db = M/V0$.

Where D_b= bulk density, V_0=initial volume of powder. Tapped density (D_t) was calculated by using tapped density apparatus, by using an equation, $Dt = M/V1$. Where, D_t= Tapped density, Vt=tapped volume. From true density and bulk density, carr's compressibility index and Hausner's ratio were calculated by the following equations.

$$\text{Carr's compressibility index} = \frac{Dt-Db}{Dt} * 100$$

$$\text{Hausner's ratio} = \frac{Dt}{Db}$$

Post compression parameters

Tablets from all the formulation batches (FH1-FH9) were evaluated for different parameters.

The average tablet's thickness was determined for 20 tablets of each batch using vernier Caliper [14]. The weight variation was determined by selecting twenty tablets from each batch randomly and their weights and average weight were found. Then individual tablet´s weight was compared with an average weight and % deviation was calculated [15]. Hardness was determined by selecting five tablets

from each formulation randomly and was checked using a Monsanto hardness tester. Then the average hardness value was determined [16]. The friability was determined for 10 tablets using Roche friabilator and % loss on friability was calculated [17]. For estimating drug content, 10 tablets of each formulation were weighed and crushed with a pestle in a glass mortar. Blend equivalent to 30 mg of Fexofenadine HCl was weighed and dissolved in phosphate buffer pH of 6.8. The solution was filtered through a 0.45 µm membrane filter and was analyzed at λmax of 259 nm using a UV spectrophotometer. Then drug content was estimated using a calibration curve [18].

Wetting time and water absorption ratio(R) [19]

Double folded tissue paper was placed in a Petri dish containing 10 ml of a dye solution. Then, a tablet was placed carefully on the surface of tissue paper and allowed to wet completely. The time taken for reaching the colored upper surface of the tablet was noted as wetting time.

The dry weight of the tablet in the above procedure before keeping it into the Petri dish was noted as Wb.

Then the weight of the wet tablet was measured and noted as Wa. The water absorption ratio (R) was calculated from the equation, $R = 100(Wa - Wb)/Wb$.

***In-vitro* disintegration time**

The disintegration time was determined by USP disintegration test apparatus using 900 ml of P^H 6.8 phosphate buffer maintained at 37±2 °C. Six tablets from each formulation batch were placed in each of the tubes and the time required for complete disintegration of the tablet was determined [20, 21].

***In vitro* dissolution studies**

In vitro dissolution studies for all formulations (FH1-FH9) and marketed tablets were carried out in triplicate and standard deviation was applied [22]. The dissolution studies were carried out using the USP paddle method at 100 rpm in 900 ml of phosphate buffer pH 6.8 as dissolution media, maintained at 37±0.5 °C. 5 ml aliquot was withdrawn at specified time intervals, 2, 4, 6, 8, 10, 15,20 min. Then, filtered through Whatman filter-paper, and absorbance was measured using a UV spectrophotometer at 259 nm. An equal volume of fresh medium, which was pre-warmed at 37 °C, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test. Then, the % drug dissolved at different time intervals was calculated using a calibration curve. Further $t_{90\%}$ and Q10 were also calculated from *in vitro* dissolution data.

Calculation of overall desirability (OD) or desirability function (DF)

The OD was used for the optimization of the formulation, as the responses have to be combined to get desired characteristics. Optimized ODTs should have low disintegration time, low $t_{90\%}$, and high Q10. The individual desirability of each formulation was calculated using the following method.

The disintegration time and $t_{90\%}$ values were minimized in the optimization procedure.

The desirability function of this response was calculated using the equation shown below [23].

$$ID1 \text{ and } ID\ 2 = Y\max - Yi / Y\max - Y\text{ target}$$

ID_1 and ID_2 = Individual desirability of disintegration time and $t_{90\%}$.

The Q10 values were maximized in the optimization procedure as optimized ODTs should have a high % of drug release. The desirability function of this response was calculated using the equation shown below.

$$ID\ 3 = Y\,i - Y\min / Y\text{ target} - Y\min$$

ID_3 = Individual desirability of Q10.

The overall desirability values were calculated from the individual desirability values by using the equation shown below

$$OD = (ID1ID2ID3 \ldots \ldots IDn)\ 1/n$$

Where n= number of desirable responses of the experiment.

Based on OD, the formulation with the highest OD was selected as the best or optimized formulation. The selected optimized formulation was used for further characterizations as shown below.

Drug-excipients compatibility studies

Drug excipient compatibility studies were conducted to find out the compatibility between drugs and excipients by FTIR and DSC analyses.

FTIR studies

Infrared spectra of pure drug sample and optimized formulation were recorded by KBr method using Fourier Transform Infra-Red Spectrophotometer (FTIR-Bruker, α ALPHA-t). The powdered sample was mixed homogeneously with dry powdered potassium bromide and then compressed into a transparent disc under high pressure ($10t/in^2$) using special dies. IR spectra were then recorded by placing this disc in an IR spectrophotometer in a scanning range of 400-4000 $cm^{-1}$and the resolution was 1 cm^{-1}[24].

Differential scanning calorimetry (DSC)

Thermal analysis was carried out for pure drug samples and optimized formulation. The sample (weighing about 5 mg) was sealed in aluminum pans hermetically and subjected to a heating rate of 10 °C/min at a temperature range of 30-300 °C. In addition, N_2 was used as purging gas at a rate of 40 ml/min. DSC thermograms of the samples were recorded using Differential Scanning Calorimeter (DSC-60, Shimadzu, Japan) with Shimadzu software programs. Indium standard was utilized to calibrate the DSC temperature and enthalpy scale [25].

***In vivo* studies**

After taking approval from the Institutional Animal Ethics committee at Malla reddy Institute of pharmaceutical sciences (1662/PO/Re/S/12/CPCSEA), Andhra Pradesh, India. Pharmacokinetic studies were conducted with optimized ODT formulation using ≈3.0 kg healthy rabbits in comparison with the marketed formulation of Fexofenadine (Allegra) and suspension of pure drug.

Experimental design

Animals were separated into four experimental groups; each group consisted of three animals (n=3) as shown in table 3. The test formulation (optimized ODT of Fexofenadine) was compared with the reference (marketed formulation, film-coated tablet of Fexofenadine, and suspension of pure drug) under fasting conditions.

Table 3: Experimental protocol for *in vivo* studies

S. No.	Group no.	No. of animals	Group name	Treatment
1	I	3	Control	Placebo
2	II	3	Test	Best Fexofenadine ODT test formulation
3	III	3	Reference 1	Reference formulation (Allegra)
4	IV	3	Reference 2	Suspension of pure drug

Drug administration and sampling procedure

The test, marketed formulation, and pure drug suspension were administered via oral gauge at a dose of 1.541 mg/kg Fexofenadine. The dose was calculated based on the conversion factor of adult dose to rabbit dose as shown in the equation below [26].

$$\text{Animal dose (mg/kg)} = \text{HED(mg/kg)} * \text{Animal Km factor/Human Km factor}$$

HED: Human Equivalent Dose, Animal Km factor=12, Human Km factor=37

Analysis of blood samples

The blood samples (each of about 2 ml) were drawn at 0, 0.5, 1, 1.5, 2, 4, 8, 12, 14, 18, and 24 h after administration of formulation from the marginal ear vein of the rabbits of all groups held in the wooden box. The collected blood samples were immediately centrifuged at 5000 rpm in an ultra cooling centrifuge for 10 min â€.4The supernatant plasma sample was separated and stored in clean screw-capped 5 ml polypropylene plasma tubes at-20˚c in a deep freezer, until further analysis [27-30].

Extraction of drug from rabbit plasma

The stored plasma samples were processed at room temperature, 250 µl of plasma was added to 500 µl of Acetonitrile to precipitate the proteins. The samples were vortexed on a vortex mixer for 15 min, followed by centrifugation at 10,000rpm for 15 min. The respective supernatant samples were injected into the HPLC column.

Development of plasma data

The area of the peak of the drug was taken from HPLC chromatogram obtained by injection of extracted plasma samples collected at different time intervals and the concentration of Fexofenadine HCl was determined by (linearity) calibration curve. Then, the plasma data for Fexofenadine HCl in different groups was obtained.

Estimation of pharmacokinetic parameters

The plasma concentrations were used to construct plasma profiles by plotting drug concentration-time curves. To determine the pharmacokinetic parameters, all data obtained subsequently were fed into pharmacokinetic software "Kinetica version 5.0". The pharmacokinetic parameters such as Cmax and tmax, AUC_0–t, Kel, $t_{1/2}$, and Ka were calculated by the residual method. The pharmacokinetic parameters were presented as mean±SD [31].

Short term stability studies [32]

In the present study, stability studies were carried out for optimized formulation by storing in stability chambers at 40 °±2 °C and RH 75%±5% for 3 mo as per International Conference on Harmonization (ICH) guidelines. The tablets were analyzed for hardness, friability, disintegration time, drug content, and *in vitro* dissolution study at 30 d intervals for 90 d after storage.

Statistical analysis

Statistical assessment of differences between two groups was performed by student's t-test and among three groups was performed by one-way Analysis of variance (ANOVA) using the Graph-pad PRISM version 5.04 software. A p-value of≤ 0.05 was considered to represent the statistical difference [33, 34].

RESULTS AND DISCUSSION

Calibration curve of fexofenadine

The scan of the drug solution in the UV region (200-400 nm) was conducted to find out the wavelength of maximum absorption (λmax). The λmax was found to be at 259 nm. So, the calibration curve of Fexofenadine was developed at 259 nm in pH 6.8 phosphate buffer (fig. 1) by plotting Concentration vs Absorbance. The calibration curve has shown a regression coefficient of 0.999, similar to the reports of Borawake Payal D *et al.* [35].

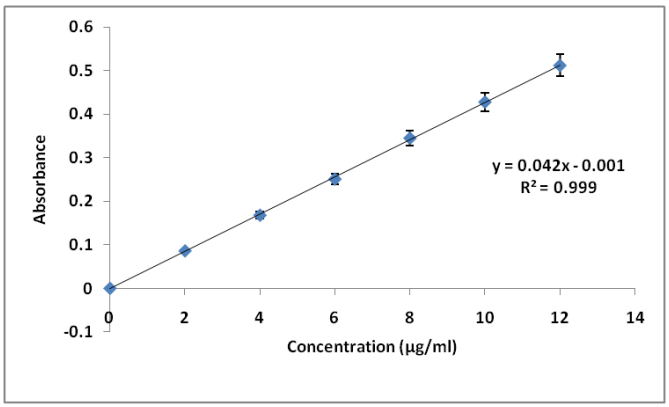


Fig. 1: Calibration curve of fexofenadine, n=3

Taste evaluation

The taste of taste-masked granules prepared with different ratios of the drug: Eudragit E100 (TFH1, TFH2, TFH3) was evaluated by taste scores of bitter intensity scale given by six volunteers. As per the scores given by volunteers, it was found that the taste score was decreased with an increasing proportion of Eudragit E100, a taste masking polymer. It indicated that the taste of the drug was effectively masked at a higher concentration of Eudragit E100 as the lower the score, the better the masking of taste.

Hence, the total score of TFH3 was least i.e., 0 and the average score was also 0 as shown in table 4 indicated that the TFH3 possessed good taste as per bitter intensity scale (table 1). So, TFH3 granules were selected as the best taste-masked granules to prepare ODT formulations of Fexofenadine.

Table 4: Scores of taste masking test

S. No.	Ratio (Drug: eudragit E100)	Scores given by 6 volunteers						Total score	Average score
		I	II	III	IV	V	VI		
1	TFH1	3	2	2	2	3	2	14	2.3
2	TFH2	1	1	1	1	2	1	07	1.16
3	TFH3	0	0	0	0	0	0	00	0

Evaluation of precompression parameters (flow properties)

The blend of the best taste-masked granules (TFH3) with all other excipients before compression into tablets were evaluated for precompression parameters i.e. angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio to find the flow properties of the blend.

The values for the angle of repose were found to be within the range of 24.36°±0.25 to 28.26°±0.14. Bulk density and tapped density of

various formulations were found to be within the range of 0.389±0.14 to 0.471±0.02 (gm/ml) and 0.456±0.02 to 0.564±0.18 (gm/ml) respectively. Carr's index was found to be within the range of 13.08±0.26 to 18.41±0.48, respectively. Hausner's ratio was within the range of 1.15±0.14 to 1.23±0.48 as shown in table 5. It was concluded that the powder blends of all formulations have fair to good flow properties, which confirmed the uniform filling during compression into tablets similar to the reports of Nirmala D *et al.* [36].

Table 5: Results of pre-compression parameters of different fexofenadine hydrochloride ODT formulations

S. No.	Parameters	Formulation code								
		FH1	FH2	FH3	FH4	FH5	FH6	FH7	FH8	FH9
1	Angle of repose ° (θ)	25.25±0.26	24.36±0.25	25.16±0.32	26.14±0.02	28.26±0.14	27.25±1.16	27.15±0.20	26.02±0.18	27.15±0.26
2	Bulk density (g/ml)	0.412±0.32	0.418±0.85	0.432±0.52	0.389±0.14	0.427±0.15	0.471±0.02	0.452±0.22	0.457±0.25	0.467±0.26
3	Tapped density (g/ml)	0.498±0.25	0.489±0.23	0.497±0.10	0.456±0.02	0.502±0.56	0.559±0.20	0.554±0.10	0.538±0.06	0.564±0.18
4	Carr's index	17.27±0.52	14.52±0.16	13.08±0.26	14.69±0.01	14.94±0.03	15.74±0.02	18.41±0.48	15.06±0.65	17.20±0.25
5	Hausner's ratio	1.21±0.26	1.17±0. 21	1.15±0.14	1.17±0. 52	1.18±0. 36	1.19±0. 25	1.23±0. 48	1.18±0. 85	1.21±0. 75

n = 3, All values represent mean±SD

Post compression parameters

The blends were compressed into tablets of 200 mg weight by direct compression [37, 38] with flat punches. Then the tablets were evaluated for post-compression parameters i.e. thickness, hardness, friability, weight variation, wetting time, water absorption ratio, *in vitro* disintegration time, *in vitro* dissolution studies, drug content, and their results are shown in table 6.

The thickness of tablets was within the range of 3.14±0.2 to 3.65±0.3 mm. Hardness for all the formulations was in the range of 3.24±0.1 to 4.85±0.01 kg/cm^2, which indicated that all the formulations possessed sufficient mechanical strength. %weight variation (0.21±0.4 to 0.91±0.12) was found to be within IP limits. Friability values i.e. % loss, were found to be less than 1% for all formulations indicated that all are within the IP limits. The wetting time of all the formulations was found to be in the range of 23±3 to 41±1 seconds and the water absorption ratio was found to be within the range of 64.20±0.22 to 89.24±0.44. Among all the formulations, the FH6 formulation has shown the least wetting time and highest water absorption ratio, which indicated that it absorbs water fast and maximum amount led to fast disintegration and dissolution of tablets. The wetting time was significantly decreased ($p \leq 0.05$) and the water absorption ratio was significantly increased ($p \leq 0.05$) as the concentration of super disintegrants increased. The % drug content of all the formulations was found to in the range of 90.25±0.26 to 98.14±0.32, which was within the specified limits. *In vitro* disintegration time of all formulations was in the range of 30±2 to 59±3 seconds. Among all the formulations (FH1-FH9), FH6 containing 9% of croscarmellose sodium as super disintegrant showed rapid disintegration with the lowest disintegration time of 30 seconds which might be due to its fast water absorption ability.

On comparison of disintegration time of tablets prepared by increased concentration of SSG (FH1-FH3) and CCS (FH4-FH6), GK (FH7-FH9), the disintegration time was significantly decreased($p \leq 0.05$) with increasing concentration of super disintegrants (table 7). Tablets prepared by CCS have shown the lowest disintegration time compared to other superdisintegrants used (SSG and GK) at all concentrations (3%, 6%, 9%). Marketed Fexofenadine tablet disintegration time was found to be 58±0.01 seconds, maybe because it is a film-coated tablet.

Table 6: Results of different *in vitro* parameters of prepared ODT formulations of fexofenadine

S. No.	Parameters	Formulation code								
		FH1	FH2	FH3	FH4	FH5	FH6	FH7	FH8	FH9
1	Thickness (mm)***	3.14±0.2	3.26±0.11	3.52±0.05	3.21±0.02	3.65±0.3	3.44±0.12	3.28±0.01	3.22±0.1	3.39±0.8
2	Hardness** (Kg/cm^2)	4.85±0.01	4.23±0.02	3.24±0.5	4.51±0.11	3.98±0.6	3.24±0.1	4.12±0.3	3.95±0.15	3.64±0.3
3	Weight variation**** (%)	0.52±0.5	0.91±0.12	0.23±0.6	0.65±0.3	0.34±0.11	0.21±0.4	0.73±0.5	0.86±0.01	0.43±0.2
4	Friability (%)***	0.42±0.07	0.52±0.02	0.15±0.01	0.25±0.01	0.36±0.03	0.14±0.03	0.25±0.06	0.41±0.05	0.85±0.03
5	Wetting time (sec)**	30±2	27±1	25±4	38±2	29±2	23±3	41±1	36±2	32±2
6	Water absorption ratio**	64.20±0.22	67.29±0.3	69.47±0.72	85.93±0.42	86.01±0.11	89.24±0.44	72.35±0.21	76.58±0.5	79.18±0.61
7	Drug content (%)***	91.32±0.25	93.20±0.52	92.14±0.26	94.23±0.14	90.25±0.26	98.14±0.32	92.63±0.32	94.25±0.14	97.85±0.36
8	Disintegration time (sec)**	52±1	43±2	35±1	48±1	38±1	30±2	59±3	56±2	45±1
9	$t_{90\%}$ (min.)*	20.3±0.11	20.4±0.24	12±0.13	20.3±0.17	21±0.31	9.3±0.28	20±0.19	18.2±0.54	20±0.57
10	Q10 (%)*	65.09±0.32	70.72±0.19	76.37±0.32	67.32±0.63	68.76±0.21	92.31±0.49	62.63±0.14	74.26±0.23	74.56±0.82
11	Overall desirability (OD)	0.1	0.23	0.65	0	0.208	1	0	0.144	0.353

****n=20, ***n=10, **n=6, *n=3, All values represent mean±SD

In vitro drug release studies

In vitro, drug release studies were conducted for all formulations and its results are shown in table 7. It revealed that the drug release rate was increased with the increasing concentration of superdisintegrants, similar to the reports of Gugulothu D *et al.* [39].

Among all the formulations, the FH6 formulation in which Croscarmellose sodium (9%) was used as super disintegrant shown the highest drug release compared to formulations prepared with other superdisintegrants. It might be due to its rapid disintegration, lowest wetting time, with the highest water absorption ratio.

Then $t_{90\%}$ and Q10 were calculated and were found within the range of 9.3±0.28 to 21±0.31 min and 62.63%±0.14 to 92.31%±0.49, which indicated that as the concentration of superdisintegrants was increased, (FH1-FH3, FH4-FH6, and FH7-FH9) $t_{90\%}$ was significantly decreased ($p \leq 0.05$) and Q10 was significantly increa sed ($p \leq 0.05$) which could be due to rapid disintegration effect at an increased concentration of superdisintegrants. In the comparison of $t_{90\%}$ and Q10 of all formulations, FH6 has shown the lowest $t_{90\%}$ and highest Q10 at the highest concentration of CCS.

The overall desirability (OD) of all the formulations was calculated to find the most desirable formulation (optimized formulation) based on the results of selected parameters i.e. disintegration time, $t_{90\%}$, and Q10. The range of OD of different formulations was from 0 to 1 (table 7). Among all formulations, FH6 has shown the highest OD i.e. '1', which confirmed that it is a desired or the best-optimized formulation.

Comparative *in vitro* %drug release profile of optimized ODT formulation with the marketed formulation

The *in vitro* % drug release studies of optimized formulation (FH6) were compared with the marketed formulation (Allegra). From the results, it was observed that the time taken for releasing 90% drug ($t_{90\%}$) was less (9.3 min±0.28) and Q10 (92.31%±0.49) was more for FH6 compared to marketed formulation (26 min±0.2) and (59.78%±0.01) respectively (table 8). It revealed the fast release of drug from optimized ODT of Fexofenadine which can lead to the rapid onset of action than the marketed Fexofenadine tablet. Then, the optimized formulation (FH6), marketed formulation, and pure drug suspensions were further compared by *in vivo* studies.

Table 7: Percentage of drug dissolved from ODT formulations of fexofenadine at different time intervals

S. No.	% drug dissolved									
	Time (min)	FH1	FH2	FH3	FH4	FH5	FH6	FH7	FH8	FH9	Marketed tablet
1	0	0	0	0	0	0	0	0	0	0	0
2	2	39.26±0.14	42.56±0.20	46.25±0.21	45.36±0.04	42.56±0.17	59.15±0.16	29.63±0.14	35.26±0.13	32.56±0.20	6.84±0.04
3	4	45.26±0.06	49.85±0.16	52.63±0.63	51.21±0.03	48.75±0.52	67.94±0.52	35.26±0.02	40.26±0.16	46.45±0.03	19.54±0.06
4	6	52.26±0.42	57.14±0.41	61.52±0.49	57.06±0.52	54.94±0.63	76.73±0.02	49.45±0.85	57.26±0.04	52.56±0.02	26.98±0.20
5	8	58.59±0.26	64.43±0.08	68.74±0.24	62.91±0.14	61.13±0.01	85.52±0.31	55.15±0.36	65.45±0.02	68.265±0.51	42.64±0.16
6	10	65.09±0.32	70.72±0.19	76.37±0.32	67.32±0.63	68.76±0.21	92.31±0.49	62.63±0.14	74.26±0.23	74.56±0.82	59.78±0.01
7	15	71.59±0.26	76.01±0.34	84.01±0.06	74.61±0.52	73.51±0.06	99.11±0.05	79.85±0.64	80.23±0.56	82.53±0.06	67.52±0.24
8	20	88.09±0.04	89.3±0.42	91.64±0.15	86.46±0.14	89.7±0.18	-------	88.63±0.02	91.26±0.14	94.63±0.21	71.46±0.11
9	$t_{90\%}$ (min.)	20.3±0.11	20.4±0.24	12±0.13	20.3±0.17	21±0.31	9.3±0.28	20±0.19	18.2±0.54	20±0.57	26±0.2
10	Q10 (%)	65.09±0.32	70.72±0.19	76.37±0.32	67.32±0.63	68.76±0.21	92.31±0.49	62.63±0.14	74.26±0.23	74.56±0.82	59.78±0.01

n = 3, All values represent mean±SD

Drug-excipient compatibility studies

FTIR studies

The FTIR spectra of the Fexofenadine pure drug and the best formulation FH6 are shown in fig. 2a and 2b, respectively and interpretations are shown in table 9. Pure Fexofenadine displayed a peak characteristic of O-H stretching vibration at 3405.46 cm^{-1}, C-H aromatic stretching at 2928.95 cm^{-1}, C-H aliphatic stretching at 2881.95 cm^{-1}, C=O stretching at 1711.43 cm^{-1}, C=C stretching at 1625.87 cm^{-1}. The spectra of the best formulation showed all characteristic peaks of pure drug indicated that the drug is compatible with excipients.

DSC

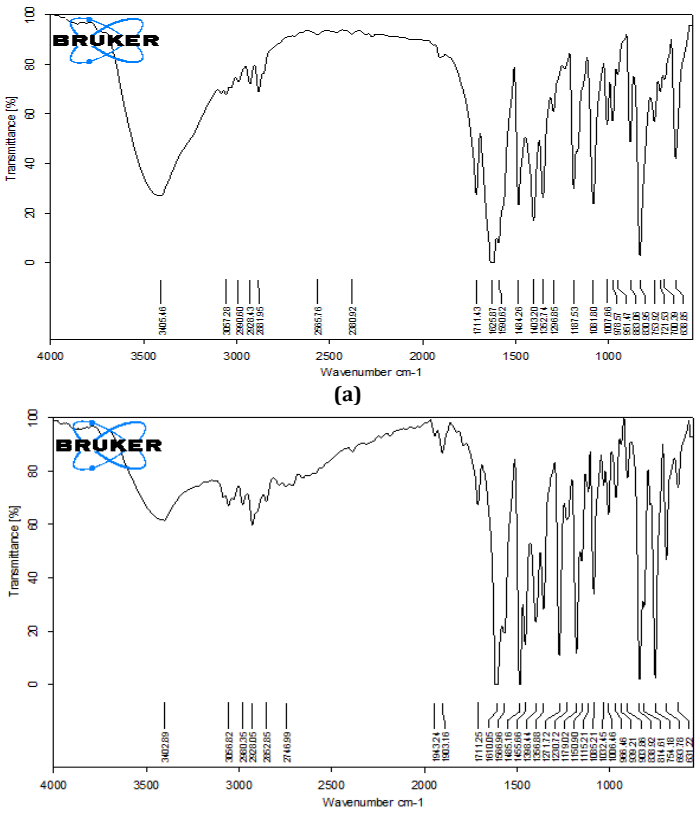
DSC thermograms were obtained for pure drug Fexofenadine and the best formulation (FH6). The DSC analysis has shown an endothermic peak at a temperature of 146-147 °C, which is a melting point of Fexofenadine in thermograms of both pure drug and ODT formulation as depicted in fig. 3 a and 3 b, respectively. It revealed that there was no difference in the endothermic peak of Fexofenadine in DSC thermograms of pure drug and best formulation, which indicates that the drug was compatible with the other formulation ingredients.

In vivo studies

By using the developed and validated HPLC method, the pharmacokinetic parameters were determined in *in vivo* studies using rabbits. The plasma concentration values at different time intervals in different groups are given in table 8 from which pharmacokinetic parameters were obtained.

The pharmacokinetic data for the Fexofenadine test, reference formulations (Allegra and pure drug suspension) are given in table 9. From the table, it was found that there was no statistically significant difference between test formulation and reference 1 and 2 formulations concerning Cmax. But there was a statistically significant difference ($p \leq 0.05$) between test and reference 1 and 2 formulations concerning tmax, $AUC_{(0-t)}$, $AUC_{(0-\alpha)}$, which confirmed that test formulation (optimized ODT of Fexofenadine) has shown significantly increased tmax along with significantly increased bioavailability compared to the marketed tablet. The obtained tmax for marketed formulation in the present study might be lesser than its actual tmax due to crushing of tablet before administration according to animal dose.

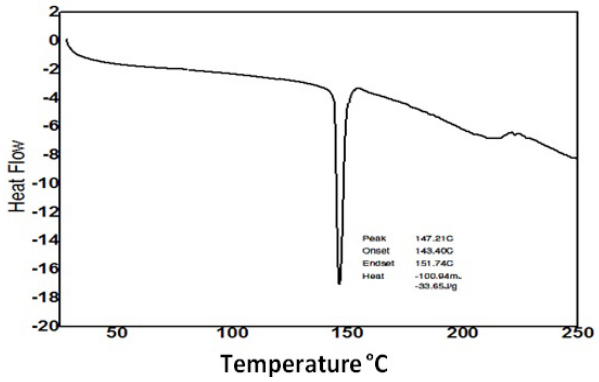
It was also found that there was a statistically significant difference between test and reference formulations concerning Ka ($p \leq 0.05$), which indicated that the test formulation (ODT of Fexofenadine) has shown a fast and increased rate of absorption though AUC was less compared to a pure drug suspension. More bioavailability of pure drug suspension could be due to low solubility, slow and prolong rate of absorption given more area under the curve. It confirmed that test formulation has shown a rapid onset of action compared to both marketed formulation and pure drug.



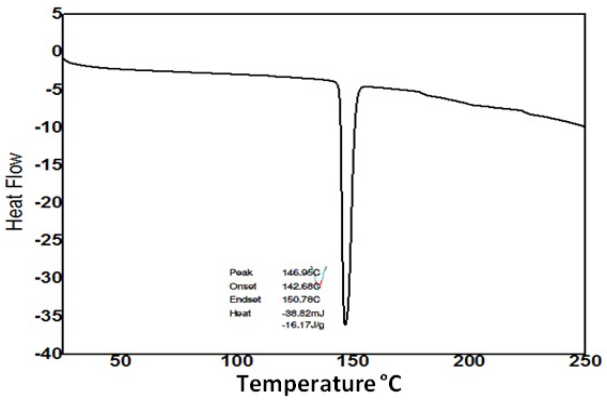
(a)

(b)

Fig. 2: FTIR spectrum of (a) pure drug (b) best ODT formulation



(a)



(b)

Fig. 3: DSC thermogram of (a) pure drug (b) best ODT formulation of Fexofenadine

Table 8: Plasma concentration values of fexofenadine in different groups

S. No.	Time (h)	Concentration (ng/ml)		
		Group II test formulation (FH6)	Group III reference I (Allegra)	Group IV reference II(Pure drug suspension)
1	0	0	0	0
2	0.5	86.92±12.46	79.82±2.54	16.06±2.95
3	1	124.36±9.52	98.18±11.20	28.63±3.26
4	1.5	108.33±6.18	112.77±6.84	35.03±1.22
5	2	91.62±8.10	79.42±16.28	49.62±3.68
6	4	74.6±3.66	57.68±10.22	61.96±1.28
7	8	52.36±8.29	42.39±4.20	81.63±0.59
8	12	36.44±14.02	36.84±6.69	101.34±3.64
9	14	29.34±11.26	29.66±3.84	121.02±4.22
10	18	22.84±3.54	22.63±2.22	92.52±4.66
11	24	18.62±10.22	12.24±7.58	58.26±5.77

n = 3, All values represent mean±SD

Table 9: Pharmacokinetic parameters of fexofenadine formulations

S. No.	Parameters	Test	Reference 1 (Allegra)	Pure drug (Pure drug suspension)
1	C max(ng/ml)	124.36±9.52	112.77±6.84	121.02±0.02
2	T(max) (hrs)	1±0.2*	1.5±0.4	14±0.11**
3	AUC (0-24)ng. h/ml	1093±3.96*	929.09±3.55	1908±3.69 **
4	AUC(0-∞)ng. h/ml	1336.5±0.2*	1068±0.03	2706.8±0.18**
5	$t_{1/2}$ (h^{-1})	9.66±0.11*	7.71±0.26	9.44±0.42
6	Kel (hrs)	0.071±0.16	0.089±0.35	0.073±0.17
7	Ka(h^{-1})	2.17±0.8*	1.55±0.3	0.05±0.0014**

n=3, All values represent mean±SD, *= $p \leq 0.05$-Comparison between test formulation and reference 1 formulation. **= $p \leq 0.05$-Comparison between test formulation and reference 2 formulations.

Comparison among test and reference formulations

The comparison data for the Fexofenadine test and reference formulations are given in table 10. From the table, it was found that the test formulation (FH6) has less disintegration time and $t_{90\%}$. The Cmax was more for test formulation compared to the marketed formulation and pure drug. The tmax of the test was less than marketed and pure drug suspension. Total bioavailability of test formulation was more when compared to the marketed formulation and was less when compared to the pure drug.

The present work aimed to get more bioavailability and rapid action with test formulation compared to reference formulation and pure drug, respectively, which was achieved from this study. Hence the prepared ODT of Fexofenadine was effectively tasted masked at 1:2 ratio of Drug: Eudragit E100 and successful using 9% Cros Carmellose Sodium as super disintegrant for rapid onset of action by the ease of swallowing.

Stability studies

From the stability studies, it was observed that the optimized tablets were found to be stable as there were no changes observed in hardness, friability, disintegration time, drug content, and *in vitro* dissolution test on storage for 90 d at specified conditions. The data for stability studies are given in table 11.

Table 10: Comparison data of fexofenadine hydrochloride ODT with reference formulation and pure drug suspension

S. No.	Parameter	Test (FH6)	Reference1 (Allegra)	Reference 2 (Pure drug)
1	Disintegration time (sec)	30±0.5*	58±0.01	----------
2	$t_{90\%}$ (min)	9.3±0.28*	26±0.12	----------
3	Q10	92.31±0.49	59.78±0.01	
3	$Cmax_{(ng/ml)}$	124.36±0.14*	112.77±0.3	121.02±0.12
4	Tmax **(**h)	1±0.2**	1.5±0.4	14±0.11
5	$AUC_{(0-24)ng.\ h/ml}$	1093.6±0.12***	929.09±0.34	1908.3±0.26
6	Ka(h^{-1})	2.17±0.8*	1.55±.3	0.05±0.0014**

n=3, All values represent mean±SD, *= $p \leq 0.05$-On comparison between test formulation vs reference1 formulation. **= $p \leq 0.05$-On comparison between test formulation vs pure drug suspension. ***= $p \leq 0.05$-On comparison among test formulation, marketed formulation, and pure drug suspension.

Table 11: Stability data for optimized formulation (FH6) of fexofenadine

S. No.	Parameter	Storage time (months)			
		0 (Initial)	1	2	3
1	Hardness (Kg/cm^2)	3.24±0.1	3.20±0.52	3.15±0.2	3.11±0.5
2	Friability(%loss)	0.14±0.03	0.16±0.11	0.18±0.35	0.19±0.2
3	Drug content (%)	98.14±0.32	98.02±0.02	98.96±0.6	98.14±0.01
4	Disintegration time(sec)	30±0.5	31.25±0.14	31.98±0.35	32.65±0.1
5	$t_{90\%}$ (min)	9.3±0.28	9.2±0.12	9.2±0.3	9.1±0.01
6	Q10 (%)	92.31±0.49	91.4±0.01	91.47±0.14	91.26±0.2

n = 3, All values represent mean±SD

CONCLUSION

ODT of Fexofenadine hydrochloride was successfully prepared by masking the bitter taste at 1:2 ratio of drug and Eudragit E100 and by 9% Croscarmellose sodium as effective super disintegrant. Optimized formulation disintegrated within 30 sec and shown about 100% of drug release within 15 min. From the pharmacokinetic studies, it was concluded that test formulation has more bioavailability, Cmax, and less tmax with a high rate of absorption than marketed formulation (film-coated tablet). Hence the optimized formulation was successful ODT with more bioavailability and rapid action.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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