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 oral mucosal 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 amn psychotic patients. There is no need for water to swallow the dosage form that is a noticeably convenient formulation 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 HC1 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.

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.

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 (THH1, TFH2, THF3) 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].

| 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 (THH1, THF2, and THF3) 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].

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

| No. | Code | Ratio |
|-----|------|-------|
| 1   | TFH1 | 1:1   |
| 2   | TFH2 | 1:1.5 |
| 3   | TFH3 | 1:2   |

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      | THF3 Granules (mg)    | 90  | 90  | 90  | 90  | 90  | 90  | 90  | 90  | 90  |
| 2      | Sodium starch Glycerate(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,

\[ \theta = \tan^{-1} \frac{h}{r} \]

θ = angle of repose, h = height of the pile of powder, r = radius of the base of the pile. Apparent bulk density (Db) was determined using bulk density apparatus by an equation, \( Db = \frac{M}{V0} \).

Where Db is bulk density, V0 = initial volume of powder. Tapped density (Dt) was calculated by using tapped density apparatus, by using an equation, \( Dt = \frac{M}{V1} \). Where, Dt = Tapped density, Vt = tapped volume.

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 A max 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 ,

\[ R = \frac{W_a - W_b}{W_b} \]

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. 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].

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 t90%, high Q10. The individual desirability of each formulation was calculated using the following method.

The disintegration time and t90% values were minimized in the optimization procedure. The desirability function of this response was calculated using the equation shown below [23].

\[ \text{ID}_2 = \frac{Y_{\text{max}} - Y_{\text{target}}}{Y_{\text{target}} - Y_{\text{max}}} \]

ID1 and ID2 = Individual desirability of disintegration time and t90%,

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.

\[ \text{ID}_3 = \frac{Y_1 - Y_{\text{target}}}{Y_{\text{target}} - Y_1} \]

ID3 = Individual desirability of Q10.

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

\[ \text{OD} = (\text{ID}_1 \times \text{ID}_2 \times \text{ID}_3) \times \frac{1}{n} \]

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, a ALPHA-T). The powdered sample was mixed homogeneously with dry powdered potassium bromide and then compressed into a transparent disc under high pressure (10t/in²) 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⁻²[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, N2 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/P/O/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      | I1        | 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].

\[ \text{Animal dose (mg/kg)} = \frac{\text{HED (mg/kg)}}{\text{Animal Km factor}} \times \text{Human Km factor} \]

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, 6, 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 at 4 °C. The 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 10,000 rpm 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 “Kinетica version 5.0”. The pharmacokinetic parameters such as Cmax and tmax, AU/C=τ, Kel, t1/2, 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].

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.

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 0.47±0.02 (gm/ml) and 0.45±0.02 to 0.56±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 Nimala 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±0.2 | 24.3±0.2 | 25.16±0.3 | 26.14±0.0 | 28.26±0.1 | 27.25±1.1 | 27.15±0.2 | 26.02±0.1 | 27.15±0.2 |
| 2      | Bulk density (g/ml)                | 0.26 ± 0.5   | 0.41±0.8±0.8 | 0.432±0.5 | 0.389±0.1 | 0.427±0.1 | 0.471±0.0 | 0.452±0.2 | 0.457±0.2 | 0.467±0.2 |
| 3      | Tapped density (g/ml)              | 0.32      | 0.35 | 0.2 | 0.2 | 4      | 5 | 2 | 2 | 5 |
| 4      | Carr’s index                       | 0.058±0.2 | 0.497±0.1 | 0.497±0.1 | 0.465±0.0 | 0.502±0.5 | 0.559±0.2 | 0.554±0.1 | 0.536±0.0 | 0.564±0.1 |
| 5      | Water absorption ratio             | 64.20±0.22 | 14.52±0.1 | 13.08±0.2 | 14.69±0.0 | 14.94±0.0 | 15.74±0.0 | 18.41±0.4 | 15.06±0.6 | 17.20±0.2 |
| 6      | Friability (%)                     | 0.12±0.0 | 0.17±0.21 | 0.15±0.14 | 0.17±0.52 | 0.18±0.36 | 0.19±0.25 | 0.23±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. 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 2.34±0.1 to 4.85±0.01 kg/cm², 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 64.2±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≤0.05) and the water absorption ratio was significantly increased (p≤0.05) as the concentration of super disintegrants increased. The % drug content of all the formulations was found to be 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≤0.05) with increasing concentration of super disintegrants (table 7). Tablets prepared by CCS have shown the lowest disintegration time compared to other super disintegrants 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±0.0 | 3.21±0.0 | 3.65±0.3 | 3.44±0.12 | 3.28±0.01 | 3.22±0.1 | 3.39±0.8 |
| 2      | Hardness** (Kg/cm²)               | 4.85±0.01 | 4.23±0.02 | 3.24±0.5 | 4.51±0.11 | 3.98±0.6 | 3.24±0.4 | 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±0.1 | 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±0.0 | 0.25±0.01 | 0.36±0.0 | 0.14±0.03 | 0.25±0.06 | 0.41±0.05 | 0.85±0.05 |
| 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±0.0 | 85.93±0.4 | 86.01±0.0 | 89.24±0.44 | 72.35±0.2 | 76.58±0.5 | 79.18±0.0 |
| 7      | Drug content (%)***              | 91.32±0.25 | 93.20±0.52 | 92.14±0.0 | 94.23±0.1 | 90.25±0.0 | 98.14±0.32 | 92.63±0.3 | 94.25±0.1 | 97.85±0.0 |
| 8      | Disintegration time (sec)**      | 52±1 | 43±2 | 35±1 | 48±1 | 38±1 | 30±2 | 59±3 | 56±2 | 45±1 |
| 9      | Dissolution time (min)*          | 20.3±0.11 | 20.4±0.24 | 12.0±13 | 20.3±0.17 | 21.0±31 | 9.30±28 | 20.0±19 | 18.2±0.54 | 20.0±57 |
| 10     | Q10 (%)**                        | 65.09±0.32 | 70.72±0.19 | 76.37±0.0 | 67.32±0.6 | 68.76±0.0 | 92.31±0.49 | 62.63±0.1 | 74.26±0.2 | 74.56±0.0 |
| 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<0.05) and Q10 was significantly increased (p<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.

| No. | S. | % drug dissolved | FH1 | FH2 | FH3 | FH4 | FH5 | FH6 | FH7 | FH8 | FH9 | Marketed tablet |
|-----|----|------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----------------|
| 1   | 0  | 0                | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0               |
| 2   | 2  | 39.26±0.14       | 42.56±0.14 | 46.25±0.14 | 45.36±0.14 | 42.56±0.14 | 59.15±0.14 | 29.63±0.14 | 35.26±0.14 | 32.56±0.14 | 6.84±0.04 |
| 3   | 4  | 45.26±0.14       | 49.85±0.14 | 52.63±0.14 | 51.21±0.14 | 48.75±0.14 | 67.94±0.14 | 49.45±0.14 | 57.26±0.14 | 52.56±0.14 | 26.98±0.20 |
| 4   | 6  | 52.26±0.14       | 57.14±0.14 | 61.52±0.14 | 57.06±0.14 | 54.94±0.14 | 76.73±0.14 | 49.45±0.14 | 57.26±0.14 | 52.56±0.14 | 26.98±0.20 |
| 5   | 8  | 58.59±0.14       | 64.43±0.14 | 68.74±0.14 | 62.91±0.14 | 61.13±0.14 | 85.52±0.14 | 55.15±0.14 | 65.45±0.14 | 68.26±0.14 | 42.64±0.16 |
| 6   | 10 | 65.09±0.14       | 70.72±0.14 | 76.37±0.14 | 67.32±0.14 | 68.76±0.14 | 92.31±0.14 | 62.63±0.14 | 74.26±0.14 | 74.56±0.14 | 59.78±0.01 |
| 7   | 15 | 71.59±0.14       | 76.01±0.14 | 84.01±0.14 | 74.61±0.14 | 73.51±0.14 | 99.11±0.14 | 79.85±0.14 | 80.23±0.14 | 82.53±0.14 | 67.52±0.24 |
| 8   | 20 | 88.09±0.14       | 89.3±0.14  | 91.6±0.14  | 86.46±0.14 | 89.7±0.14  | ------      | 88.63±0.14 | 91.26±0.14 | 94.63±0.14 | 71.46±0.11 |
| 9   | $t_{90\%}$ (min.) | 20.3±0.13     | 20.4±0.13  | 12±0.13    | 20±0.13    | 21±0.31    | 9±0.28      | 20±0.19    | 18±0.2    | 20±0.57    | 2±0.2 |
| 10  | Q10 (%)        | 65.09±0.14    | 70.72±0.14 | 76.37±0.14 | 67.32±0.14 | 68.76±0.14 | 92.31±0.14 | 62.63±0.14 | 74.26±0.14 | 74.56±0.14 | 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 cm⁻¹, C=O aromatic stretching at 2928.95 cm⁻¹, C=O 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 the 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 the 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 $C_{\text{max}}$. But there was a statistically significant difference (p<0.05) between test and reference 1 and 2 formulations concerning tmax, AUC (0→t), AUC (0→∞) 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 ($p < 0.05$), 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.
Fig. 2: FTIR spectrum of (a) pure drug (b) best ODT formulation

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) | Group II test formulation (FH6) | Group III reference I (Allegra) | Group IV reference II (Pure drug suspension) |
|--------|----------|--------------------------------|-------------------------------|---------------------------------------------|
| 1      | 0        | 86.92±1.246                   | 79.82±2.54                   | 16.06±2.95                                 |
| 2      | 0.5      | 124.36±6.92                   | 91.42±16.28                  | 28.63±3.26                                 |
| 3      | 1        | 98.18±11.20                   | 112.77±6.84                  | 35.03±1.22                                 |
| 4      | 1.5      | 108.33±6.18                   | 9.44±0.42                    | 49.62±3.68                                 |
| 5      | 2        | 74.36±3.66                    | 42.59±4.20                   | 61.96±2.28                                 |
| 6      | 4        | 36.44±14.02                   | 101.34±3.64                  | 81.63±0.59                                 |
| 7      | 8        | 74.6±3.66                     | 112.77±6.84                  | 124.36±9.52                                |
| 8      | 12       | 29.34±11.26                   | 91.40±3.64                   | 124.36±9.52                                |
| 9      | 14       | 22.84±3.54                    | 91.40±3.64                   | 124.36±9.52                                |
| 10     | 18       | 18.62±10.22                   | 91.40±3.64                   | 124.36±9.52                                |
| 11     | 24       | 124.36±9.52                   | 91.40±3.64                   | 124.36±9.52                                |

n = 3, All values represent mean±SD, *p ≤ 0.05-Comparison between test formulation vs reference 1 formulation. **p ≤ 0.05-Comparison between test formulation vs pure drug suspension.

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 t90%. 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% Caromellose 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 9: Pharmacokinetic parameters of fexofenadine formulations

| S. No. | Parameters | Test | Reference 1 (Allegra) | Pure drug (Pure drug suspension) |
|--------|------------|------|-----------------------|----------------------------------|
| 1      | Cmax (ng/ml) | 124.36±9.52 | 112.77±6.84 | 121.02±0.02                      |
| 2      | T(max) (hrs) | ±0.2* | 1.5±0.4 | 14±0.11**                        |
| 3      | AUC(0-24h) ng/h/ml | 1093.6±0.34 | 929.09±3.55 | 1908±3.69**                      |
| 4      | AUC(0-∞) ng/h/ml | 1336.5±0.2* | 1068±0.03 | 2706.8±0.19**                     |
| 5      | t1/2 (h^-1) | 9.66±0.11* | 7.71±0.26 | 9.44±0.42                        |
| 6      | Ke (hrs)    | 0.07±0.16 | 0.08±0.35 | 0.07±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 ≤ 0.05-Comparison between test formulation vs reference 1 formulation. **p ≤ 0.05-Comparison between test formulation vs pure drug suspension.

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

| S. No. | Parameter | Test (FH6) | Reference 1 (Allegra) | Reference 2 (Pure drug) |
|--------|-----------|------------|----------------------|-------------------------|
| 1      | Disintegration time (sec) | 30±0.5* | 58±0.01 | ---                  |
| 2      | t90 (min) | 9.3±0.28* | 26.0±0.12 | ---                  |
| 3      | Q10 | 92.31±0.49 | 59.78±0.01 | 121.02±0.12            |
| 4      | Cmax (ng/ml) | 124.36±9.52 | 112.77±6.84 | 121.02±0.12            |
| 5      | Tmax (h) | 1.5±0.4 | 14±0.11 | 14±0.11               |
| 6      | AUC(0-24h)ng/h/ml | 1093.6±0.34 | 929.09±3.55 | 1908±3.69**            |
| 7      | Ka (h^-1) | 2.17±0.8* | 1.55±0.3 | 0.05±0.0014**          |

n=3, All values represent mean±SD, *p ≤ 0.05-Comparison between test formulation vs reference 1 formulation. **p ≤ 0.05-Comparison between test formulation vs pure drug suspension. ***p ≤ 0.05-Comparison between test formulation vs marketed formulation.

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

| S. No. | Parameter | Storage time (months) |
|--------|-----------|-----------------------|
| 1      | Hardness (Kg/cm²) | 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±0.05 | 0.19±0.02 |
| 3      | Drug content (%) | 98.14±0.32 | 98.02±0.02 | 98.96±0.16 | 98.14±0.01 |
| 4      | Disintegration time (sec) | 30±0.5 | 31.25±0.14 | 31.98±0.35 | 32.65±0.1 |
| 5      | t90 (min) | 9.3±0.28 | 9.2±0.12 | 9.2±0.3 | 9.1±0.01 |
| 6      | Q10 (%) | 92.31±0.49 | 91.47±0.14 | 91.26±0.2 |

n = 3, All values represent mean±SD.
CONCLUSION
ODT of Cefuroxime axetil was successfully prepared by masking the bitter taste at 1:3 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.

ACKNOWLEDGMENT
We are grateful to the Sri Venkateswara college of pharmacy, Hyderabad for providing the necessary chemicals and equipment to carry out the work. We thank Spectrum labs, Hyderabad for allowing us to work on rabbits.

FUNDING
Nil

AUTHORS CONTRIBUTIONS
All authors have contributed equally.

CONFLICTS OF INTERESTS
Declared none

REFERENCES
1. Sreenivas SA, Sandagi PM, Gadad AP. Orodispersible tablets: new-fangled drug delivery system-a review. Int J Pharm Educ Res 2005;3:177-80.
2. Setty CM, Prasad DV, Gupta VRM. Development of fast dispersible Aclofenac tablets: effect of the functionality of superdisintegrants. Int J Pharm Sci 2008;7:180–5.
3. Raghendra RNG, Ketan T, Sunjani B. Formulation and evaluation of fast dissolving tablet of metoprolol tartrate. Int J Pharm Clin Res 2010;2:40–5.
4. Shweta SG, Tapar KK, Borse MD, Ghuge RA. Taste masking and characterization of diphenhydramine hydrochloride by spray-drying technique. Int J Pharm Res Dev 2010;1:7–10.
5. Kartikeyan M, Mukhtar UAK, Megha M, Shadeer HP. Formulation of diclofenac tablets for rapid pain relief. Asia Pacific J Trop Dis 2012;2:308–11.
6. Kawano Y, Ino A, Sasatsu M, Machida Y, Onishi H. Preparation and evaluation of taste-masked orally disintegrating tablets with granules made by the wet granulation method. Yakugaku Zassi 2011;130:737-42.
7. Liew KB, Tan YTF, Peh KK. Characterization of oral disintegrating film containing Donepezil for Alzheimer’s disease. AAPS PharmSciTech 2012;13:134-42.
8. Audha SH, Elbadry M, Ibrahim MA. Design, formulation, and characterization of fast dissolving films containing dextromethorphan. Dig J Nanomater Bios 2014;9:133-41.
9. Naresh Kumar K, Sandeep D. Formulating taste-masked orally disintegrating tablets of a bitter drug Ibuprofen. Int Res J Pharm 2013;4:71-81.
10. Preethi GB, Sayan B, Shivanukumar NH, Ravi Kumar M. Formulation of fast-dissolving tablets of doxazosin mesylate drug by direct compression method. Int J Appl Pharm 2017;9:22-8.
11. United States Pharmacopeia Convention. United States Pharmacopeia and National Formulary (USP 34-NF29) United States Pharmacopeia Convention; 2011.
12. Shah D, Shah Y, Rampradhan M. Development and evaluation of controlled release diltiazem hydrochloride microparticles using cross-linked polyvinyl alcohol. Drug Dev Ind Pharm 1997;23:567-74.
13. Kotiya GM, Patel BA, Patel KN, Patel MM. Formulation and characterization of sustained release matrix tablets of ibradine using 32 factorial designs. Int J Pharm 2018;10:59-66.
14. Adedokun M, Onah BE, Attama AN. Physico-mechanical and release properties of sustained-release artesunate tablets in hydroxypropyl methylcellulose matrix. Int J Appl Pharm 2018;10:103-8.
15. Agarwal G, Agarwal S, Karar PK, Goyal S. Oral sustained-release tablets: an overview with a special emphasis on matrix tablet. Am J Adv Drug Delivery 2017;5:64-76.
16. Arora P, Arora V. Orodispersible tablets: a comprehensive review. Int J Pharm Sci Rev Res 2012;3:270-84.
17. Nawale RB, Mohite KP. Formulation and evaluation of domperidone orodispersible tablet. Int J Pharm Sci Res 2013;4:3670-7.
18. Dash TR, Verma P. Matrix tablets: an approach towards oral extended-release drug delivery. Int J Pharm Sci Rev Res 2013;2:12-24.
19. Furtado S, Deveswaran R, Bharath S, Basavaraj BV, Abraham S, Madhavan V. Development and characterization of orodispersible tablets of famotidine containing a subliming agent. Trop J Pharm Res 2009;8:153-9.
20. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol 1975;27:46-9.
21. Radke JS, Jadhav KJ, Chajed MR. Formulation and evaluation of oro dispersible tablets of buscopan. Int J Chem Eng 2014;1:273-90.
22. Hardy JG, Healey JN, Reynolds JR. Evaluation of an entericoated delayed-release 5-aminosalicylic acid tablet in a patient with inflammatory bowel disease. Aliment Pharmacol Ther 1987;1:273-90.
23. Paterakis PG, Korainianti ES, Dallas PP, Rekkas DM. Evaluation and simultaneous optimization of some pellets characteristics using a 3 factorial design and the desirability function. Int J Pharm 2000;22:148-56.
24. Ferreira SL, Bruns RE, da Silva EG. Statistical designs and response surface techniques for the optimization of chromatographic systems. J Chromatogr A 2007;1158:2-14.
25. Swain S, Behera A, Dinda SC, Patna CN, Srutij J, Beg SA, et al. Formulation design, optimization, and pharmacodynamic evaluation of sustained-release mucosalhesive microcapsules of venlafaxine hydrochloride. Indian J Pharm Sci 2014;76:534-63.
26. Ghosh MN. Fundamentals of experimental pharmacology. 3rd edn. SK Ghosh Publications, Kolkata; 2005. p. 192–4.
27. Kauss T, Gaudin K, Gaubert A. Screening pediatric rectal forms of Azithromycin as an alternative to oral or injectable treatment. Int J Pharm 2012;436:624-30.
28. Zeng F, Wang L, Zhang W, Shi K, Zeng L. Formulation and in vivo evaluation of orally disintegrating tablets of Clozapine/Hydroxypropyl-beta-cycloextrin inclusion complexes. AAPS PharmSciTech 2013;14:854-60.
29. Xu H, Le L, Nie S, Guan J, Zhang X, Yang X, Pan W. Optimized preparation of Winprofetine proliposomes by a novel method and in vivo evaluation of its pharmacokinetics in New Zealand rabbits. J Controlled Release 2009;140:61-8.
30. Haoping X, Min S, Ying Liu Y, Jiang J, Tao MA. A novel in situ gel formulation of ranitidine for oral sustained delivery. Biomol Ther 2014;22:161-5.
31. Matter KM. Impact of pregnancy on Zonisamide pharmacokinetics in rabbits. Biomed Res Int 2013;2014:3:327-30.
32. European Council. European Pharmacopoeia. 4th ed. Strasbourg; 2002.
33. Bolton S, Bon C. Rev and expanded. 4th ed. Marcel Dekker Inc. New York: Pharmaceutical statistics and practical and clinical application; 2004. p. 96-146.
34. Singh B, Kumar R, Ahuja N. Optimizing drug delivery systems using systematic Design of experiments. Part-I: fundamental aspects. Crit Rev Ther Drug 2005;22:27-105.
35. Borawake Payal D, Kauliya A, Jitendraprasad P. Formulation of solid dispersions for enhancement of solubility and dissolution rate of simvastatin. Int J Pharm Sci Res 2012;13:94-100.
36. Nirmala D, Vidyavathi M. Preparation and evaluation of fast dissolving tablets of pitavastatin by 3 factorial design. Int J Pharm 2020;12:108-14.
37. Chen H, Aburab A, Sun CC. Direct compression tablet containing 99% active ingredient-a tale of spherical crystallization. J Pharm Sci 2019;108:1396-400.
38. Cantor SL, Augsburger LL, Hoag SW, Gerhardt A. Pharmaceutical granulation processes, mechanism and the use of binders. In: Augsburger LL, Hoag SW. editors. Pharmaceutical dosage forms: tablets. 3rd ed. London: CRC Press; 2008. p. 261-302.
39. Gugulothu D, Suraj Kumar C. Design and \textit{in vitro} evaluation of floating drug delivery system of glipizide using a combination of natural mucilages and synthetic polymers. Int J Pharm Pharm Sci 2021;13:40-8.