FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF FEXOFENADINE HYDROCLORIDE

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ABSTRACT
The purpose of current study was to enhance the solubility and dissolution rate of fexofenadine HCl by co-grinding with different diluents. Simplex lattice design was utilized in the present study. The amount of diluent- X₁ (D-mannitol), X₂ (lactose), X₃ (MCC) were selected as independent variables. Average particle size (Y₁), saturation solubility (Y₂) and the amount of drug release in 5 min (Y₃) were taken as the responses. In each diluent mixture, appropriate amount of fexofenadine HCl mixed. These mixtures were co-ground by ball mill for two different time intervals (3hrs and 6hrs). Prepared physical mixtures and various co-ground mixtures were evaluated for different densities, flow property, average particle size, drug content, saturation solubility, in vitro dissolution study. From the results co-ground mixture AB-II (D-mannitol, lactose and drug co-ground for 6 hrs) was found to be optimized. FTIR and DSC study shows that there was no any interaction between drug and excipients. Contour plot, overlay contour and response surface plot of the variables were prepared by statistic-7. Mouth Dissolving Tablet of optimized co-ground mixture was prepared by direct compression method using sucralose as sweetener and crospovidone as superdisintegrant. Prepared MDTs were evaluated for different pre-compression parameters and different post-compression parameters. All evaluation parameters were passed by prepared MDTs. There was enhancement of solubility of fexofenadine HCl and dissolution rate thus the MDTs shown faster release.

KEYWORDS: Fexofenadine HCl, Co-grinding, Simplex lattice, Mouth Dissolving Tablet.

INTRODUCTION
Poorly water-soluble drugs often show low bioavailability when administered orally because the dissolution of the drug in the gastrointestinal tract is usually the rate-limiting step. Therefore, it is important to enhance their dissolution rate for such drugs. To enhance the dissolution rate, increasing the drug solubility is necessary according to the Noyes–Whitney equation. Enhancement of the aqueous dissolution rate and/or the aqueous solubility of poorly water-soluble drugs are one of the most key topics in pharmaceutics. Several techniques have been employed in attempt to improve drug dissolution; namely micronization, solid dispersion, solvent deposition, ordered mixtures, roll-mixing and complexation. The size reduction method
has also been extensively utilised (1) because the increase in surface area can enhance the
dissolution rate and consequently the bioavailability of pharmaceutical materials. Size
reduction of pharmaceutical materials is often performed by the dry milling process. In
preparing powdered products, grinding is generally used for reducing particle size since the
dissolution rate is strongly affected by particle size. It has been reported that a strong force
(such as grinding) may increase the surface free energy and cause distortion of the crystal
lattice as well as reducing particle size. However, grinding of hydrophobic drugs usually causes
an aggregation of drug particles and consequently also limits size reduction to around 3μm.
Size reductions in nanometer range must be carried out by other techniques such as salt-assisted
milling. Researchers have explored particle size reduction to the submicron region by co-
grinding with additives (2, 3).
In this research work size reduction was done by ball mill and additives like diluents (D-
mannitol, lactose monohydrate, microcrystalline cellulose) were co-ground with drug
fexofenadine HCl.
Fexofenadine HCl, is a non-sedating anti histamine used in the symptomatic relief of allergic
conditions including seasonal allergic rhinitis and urticaria. It reduces the severity of the
symptoms associated with those conditions, providing relief from repeated sneezing, runny
nose, itchy eyes and general body fatigue. It is BCS Class II drug having low solubility. It has
bitter taste.
For the past one decade, there has been an enhanced demand for more patient friendly and
compliant dosage forms. As a result, the demand for developing new technologies has been
increasing annually. Since the development cost of a new drug molecule is very high, efforts
are now being made by pharmaceutical companies to focus on the development of new drug
dosage forms for existing drugs with improved safety and efficacy together with reduced
dosing frequency, and the production of more cost effective dosage forms. Recently, fast
disintegrating drug delivery systems have started gaining popularity and acceptance as new
drug delivery systems, because they are easy to administer and lead to better patient
compliance. In some cases such as motion sickness, sudden episodes of allergic attacks or
coughing and unavailability of water, swallowing conventional tablets may be difficult.
Particularly the difficulty is experienced by paediatrics and geriatric patients. To overcome
such problems, mouth dissolving drug delivery systems have emerged as an alternative dosage
form. Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of
a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance.

**Mouth Dissolving tablet (MDT):** These are the tablets which dissolve or disintegrate quickly in the saliva to show their action within few seconds without the help of water. A mouth dissolving tablet mainly dissolves in the mouth within 15 sec-3 min. MDT is also known as fast disintegrating tablet, fast dissolving, rapid-dissolve, quick disintegrating, orally disintegrating, rapimelt, fast melts, orodispersible, melt-in-mouth, quick dissolving, and porous tablets.

Conventional fexofenadine HCl tablet available in the market are not suitable for acute allergic conditions where quick onset of action of drug is required. Other formulation like suspension having stability problem, Furthermore fexofenadine HCl having low solubility and dissolution rate so to improve the solubility and dissolution rate, various co ground mixtures of drug with different diluents were prepared by ball mill. So to improve onset of action, dissolution behavior, stability and patient compliance fexofenadine HCl formulated as mouth dissolving tablet.

**MATERIALS AND METHODS**
Fexofenadine HCl was kindly donated from Ind-Swift laboratory Ltd. (Mumbai, India), D-mannitol and potassium di hydrogen phosphate were purchased from Sisco Research laboratories Pvt. Ltd. (Mumbai, India), lactose monohydrate and talc were purchased from Suvidhinath laboratories (Baroda, India), microcrystalline cellulose was purchased from Loba Chemicals Pvt. Ltd. (Mumbai, India), crospovidone was purchased from Yarrow chem. products (Mumbai, India), methanol was purchased from RFCL limited (New Delhi, India), di potassium hydrogen phosphate and sucralose were purchased from HiMedia Laboratories Pvt. Ltd. (Mumbai, India), potassium bromide was purchased from Merck specialities Pvt. Ltd. (Mumbai, India), sodium chloride and magnesium stearate were purchased from Molychem (Mumbai, India).

**METHODS**

**Preparation of co ground mixtures by simplex lattice design**
Simplex lattice design was utilized in the present study. In this design three factors were evaluated and experimental trials were carried out in different combination. The amount of diluent $X_1$(D-mannitol), $X_2$ (lactose monohydrate), $X_3$ (microcrystalline cellulose) were selected as independent variables. Average particle size ($Y_1$), saturation solubility ($Y_2$) and the amount of fexofenadine HCl release in 5 min-CPR ($Y_3$) were taken as the responses. A statistical model incorporating 7 interactive terms were used to evaluate the responses.

$$Y = \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{23}X_2X_3 + \beta_{13}X_1X_3 + \beta_{123}X_1X_2X_3$$
Where Y is dependent variable, $\beta_1$ is the estimated coefficient for the factor $X_1$. The mean effects ($X_1, X_2, X_3$) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($X_1X_2, X_2X_3, X_1X_3, X_1X_2X_3$) show how the response changes when two or more factors are simultaneously changes. The statistical analysis of the simplex lattice design batches was performed by multiple linear regression analysis using Microsoft excel.

### Table I Code representation of formulation

<table>
<thead>
<tr>
<th>Factorial code</th>
<th>Batch code</th>
<th>Component fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D-Mannitol ($X_1$)</td>
</tr>
<tr>
<td>A</td>
<td>A-I</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>B-I</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>C-I</td>
<td>0</td>
</tr>
<tr>
<td>AB</td>
<td>AB-I</td>
<td>0.5</td>
</tr>
<tr>
<td>BC</td>
<td>BC-I</td>
<td>0</td>
</tr>
<tr>
<td>AC</td>
<td>AC-I</td>
<td>0.5</td>
</tr>
<tr>
<td>ABC</td>
<td>ABC-I</td>
<td>0.333</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Real values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent</td>
<td>1</td>
</tr>
<tr>
<td>D-Mannitol ($X_1$)</td>
<td>110 mg</td>
</tr>
<tr>
<td>Lactose monohydrate ($X_2$)</td>
<td>110 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose ($X_3$)</td>
<td>110 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Desired response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average particle size ($Y_1$)</td>
<td>Minimum (4-7 μm)</td>
</tr>
<tr>
<td>Saturation solubility ($Y_2$)</td>
<td>Maximum (6-8 mg/ml)</td>
</tr>
<tr>
<td>Drug release in 5 minutes ($Y_3$)</td>
<td>Maximum (&gt; 80 %)</td>
</tr>
</tbody>
</table>

According to simplex lattice design diluent mixtures were prepared, in each diluent mixture, appropriate amount of fexofenadine HCl mixed. These mixtures were co ground by ball mill loaded with 14 stainless steel ball media and operated with 90 rpm for two different time
intervals (3hrs and 6hrs). Prepared co ground mixtures were evaluated for different parameters. In simplex lattice design seven batches were formed and each batch was co ground for two different time intervals (3hrs and 6hrs).

**Evaluation of physical mixtures and co ground mixtures**

**Characterization of fexofenadine HCl and co ground mixtures**

**Thermal analysis**

Differential Scanning Calorimetry (DSC) of drug and co ground mixture was carried out using aluminum sample pans at scanning speed of 10°C/min over a temperature range of 35 to 250 °C under nitrogen using differential scanning calorimeter (Shimadzu, DSC 60, TSW 60, Japan) (4).

**Fourier Transform Infrared Spectroscopy**

The drug, polymer and co ground mixture were subjected to IR spectroscopy to check the drug polymer interaction using FTIR (Thermo scientific) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1: 100. The disc was placed in the sample holder and scanned from 4000 to 400 cm⁻¹ (5).

Prepared physical mixtures and co ground mixtures were evaluated for angle of repose, bulk density, tapped density, Carr’s compressibility index, Hausner’s ratio (6).

**Particle size analysis**

Particle size analysis of physical mixtures and milled co ground mixtures were done by objective micrometer (Erma, Tokyo, Japan) equipped with optical microscope (Magnus MLX-DX, Olympus (India) Pvt Ltd, New Delhi). Average particle size was measured.

**Drug content**

Drug content was determined by dissolving co ground mixture equivalent to 30 mg of drug in 100 ml Phosphate Buffer Saline (PBS) pH 6.8(5% methanol) and samples were analyzed by UV-spectrophotometer (Shimadzu pharmaspec. UV-1800, Japan) at 259 nm (7).

**Saturation solubility study**

Saturation solubility study was performed in triplicate according to the method reported by Higuchi and Connors. Excess amount of pure drug and co ground mixture were added to 20 ml PBS pH 6.8 (5% methanol) in a screw-cap tube and shaken in a rotary flask shaker at room temperature for 48 hrs After equilibrium, aliquots were withdrawn, followed by centrifugation at 4000 rpm for 10 min and filtration. After suitable dilution the amount of drug solubilised was determined at 259 nm by UV-spectrophotometer (7-9).
**In vitro dissolution study**

*In-vitro* dissolution study was performed using USP Type I dissolution apparatus (Basket type) at speed of 50 rpm. A weighed amount of co ground mixture equivalent to 30 mg of fexofenadine HCl was filled into a basket, 250 ml of PBS pH 6.8(5% methanol) was utilized as dissolution medium. The temperature of the medium was maintained at 37 ± 0.5°C. Aliquot of dissolution medium (5 ml) were withdrawn at specific time intervals (5, 10, 15, 20, 25, 30, 35, 40 45, 50, 55, 60 min) and filtered each with whatman filter paper. Equal amount of fresh dissolution medium was replaced immediately after each withdrawal. The amount of drug present in each sample was determined by UV- spectrophotometer at 259 nm (8).

**Preparation of MDTs**

MDTs of fexofenadine HCl were prepared by direct compression method.

<table>
<thead>
<tr>
<th>Table II Composition of MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredients</strong></td>
</tr>
<tr>
<td>Co ground mixture</td>
</tr>
<tr>
<td>Crospovidone</td>
</tr>
<tr>
<td>Sucralose</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Talc</td>
</tr>
</tbody>
</table>

The optimized co ground mixture of drug and diluents were passed through sieve (#80) to ensure better mixing. Crospovidone used as super disintegrating agent and sucralose used as sweetening agent. The powder mixture was compressed using a rotary 6 station tableting machine (Hardik engineering Pvt.Ltd, Ahmedabad, India) equipped with round, flat and plain punches.

**Evaluation of MDTs**

Tablets were subjected to following quality control test (10).

**Pre compression parameters of powder blend**

Prepared powder blend was evaluated for angle of repose, bulk density, tapped density, Carr’s index and Hausner ratio.

**Post-compression parameters of MDTs**

Prepared MDTs were evaluated for following parameters:

**General Appearance**
The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance and tablet's size, shape, colour, presence or absence of an odour, 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.

**Tablet thickness**

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using digital vernier calliper.

**Weight variation**

20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

**Hardness**

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester. Three tablets were tested randomly and the average reading was noted (11).

**Friability (F)**

Friability of the tablet determined using friabilator (Elecrolab. EF-2 friabilator). This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. According to the British Pharmacopoeia, 2010, pre -weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. The friability (F) is given by the formula.

\[
\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

**Wetting Time**

Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded
twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water and the time for complete wetting is measured.

**Water absorption Ratio**

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio $R$, was determined using following equation,

$$R = 100 \left( \frac{W_a - W_b}{W_b} \right)$$

Where, $W_a$ is weight of tablet before water absorption & $W_b$ is weight of tablet after water absorption.

**Disintegration test**

Tablets were placed in each tube of disintegration apparatus. Tablet rack of the disintegration apparatus was positioned into a 1000 ml beaker and the time of disintegration was recorded. To discriminate between the formulations disintegration was done at room temperature and disk was used for the study (12).

**In vitro dispersion time**

*In vitro* dispersion time was measured by dropping a tablet in a beaker containing 50 ml of PBS pH 6.8. Three tablets from formulation were randomly selected and *in vitro* dispersion time was performed.

**Drug content**

10 tablets were weighted and powdered, powder equivalent to 30 mg of fexofenadine HCl was weighted and dissolved in PBS pH 6.8 (5% methanol) and filtered through whatman filter paper. The filtrate was collected and if requires diluted to sufficient amount with PBS pH 6.8 (5% methanol) till the concentration of the drug lies within the standard plot range. This solution was analyzed for the fexofenadine HCl at 259 nm using UV- spectrophotometer, using PBS pH 6.8 (5% methanol) as a blank (4).

**In vitro Dissolution test**

*In-vitro* dissolution study of optimized tablet was performed using USP Type II dissolution apparatus (Paddle type) at speed of 50 rpm. 250 ml of PBS pH 6.8 was utilized as dissolution medium. The temperature of the medium was maintained at 37 ± 0.5°C. Aliquot of dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10,12,14,16 min) and filtered each with whatman filter paper. Equal amount of fresh dissolution medium was
replaced immediately after each withdrawal. The amount of drug present in each sample was determined by UV-Visible spectrophotometer at 259 nm (4).

**Stability testing of drug (temperature dependent stability studies)**
The MDTs were packed in suitable packaging and stored at normal room temperature for their stability study. The tablets were withdrawn after a period of 30 days and analyzed for physical characterization (Visual defects, hardness, friability, disintegrations and dissolution etc.) and drug content.

**RESULTS**
The DSC curves of fexofenadine HCl revealed a single, sharp endothermic peak at 206 °C corresponding to the melting point (4). The DSC thermogram of co ground mixture (containing fexofenadine HCl, D-mannitol and lactose) shown the characteristic peaks corresponding to their respective melting point (fig. 1).

![DSC analysis](image)

**Fig. 1.** DSC analysis of drug and excipients for interaction studies
(A) Fexofenadine HCl, (B) Co ground mixture of fexofenadine HCl, D-mannitol and lactose monohydrate, (C) final formulation
In the FTIR spectrum of fexofenadine HCl the characteristic peaks corresponding to aromatic C-H bending (648, 667, 695, 701, 744, 776, 854 cm$^{-1}$), carboxyl C=O stretching (1704 cm$^{-1}$), C-N stretching (1279 cm$^{-1}$), -OH group (3295 cm$^{-1}$) were identified (fig. 2).

![Fig. 2. Comparison of FTIR spectra of drug and excipients for interaction studies](image)

(A) Fexofenadine HCl, (B) Co ground mixture of fexofenadine HCl, D-mannitol and lactose monohydrate, (C) D-mannitol, (D) Lactose monohydrate, (E) Crospovidone, (F) Sucralose, (G) final formulation

**Pre compression parameters**

Co ground mixtures were characterized for angle of repose, bulk density, tapped density, Carr’s compressibility index and Hausner’s ratio. Results are shown in the table III.

**Table III Pre-compression parameters of various co ground mixtures (3 hrs and 6 hrs)**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
<th>Angle of repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-I</td>
<td>0.39</td>
<td>0.5</td>
<td>21.06</td>
<td>1.26</td>
<td>40.03</td>
</tr>
<tr>
<td>B-I</td>
<td>0.5</td>
<td>0.63</td>
<td>20</td>
<td>1.25</td>
<td>39</td>
</tr>
<tr>
<td>C-I</td>
<td>0.44</td>
<td>0.58</td>
<td>23.53</td>
<td>1.31</td>
<td>40.69</td>
</tr>
<tr>
<td>AB-I</td>
<td>0.41</td>
<td>0.57</td>
<td>20.69</td>
<td>1.38</td>
<td>38.65</td>
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<tr>
<td>AC-I</td>
<td>0.37</td>
<td>0.46</td>
<td>19.99</td>
<td>1.31</td>
<td>38.30</td>
</tr>
<tr>
<td>ABC-I</td>
<td>0.44</td>
<td>0.53</td>
<td>17.64</td>
<td>1.21</td>
<td>36.50</td>
</tr>
<tr>
<td>BC-I</td>
<td>0.53</td>
<td>0.68</td>
<td>21.42</td>
<td>1.27</td>
<td>36.12</td>
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<tr>
<td>A-II</td>
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<td>0.53</td>
<td>17.66</td>
<td>1.21</td>
<td>36.86</td>
</tr>
<tr>
<td>B-II</td>
<td>0.39</td>
<td>0.5</td>
<td>21.06</td>
<td>1.26</td>
<td>36.42</td>
</tr>
<tr>
<td>C-II</td>
<td>0.46</td>
<td>0.57</td>
<td>18.75</td>
<td>1.23</td>
<td>35.75</td>
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<tr>
<td>AB-II</td>
<td>0.36</td>
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<td>17.14</td>
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<td>34.60</td>
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<td>AC-II</td>
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<td>BC-I</td>
<td>0.47</td>
<td>0.57</td>
<td>18.75</td>
<td>1.23</td>
<td>36.12</td>
</tr>
</tbody>
</table>
**Particle size analysis**

A significant decrease in particle size was obtained in the case of AB-II co ground mixture. Comparison of average particle size of physical mixtures and co ground mixtures was shown in fig. 3 (A).

**Drug content**

The percentage of drug content for all the physical mixtures and the co ground mixtures were found in the range of 96.06 % and 99.46%.

**Saturation solubility study**

Fexofenadine HCl has saturation solubility of 3.256 mg/ml. A significant increase in solubility was obtained in the case of AB-II co ground mixture. Comparison of saturation solubility of pure drug, physical mixtures and co ground mixtures was shown in fig. 3 (B).

![Graph (A)](image)

**Fig. 3.** (A) Average particle size and (B) Saturation solubility of the pure drug, physical mixtures and various co ground mixtures (± S.D. n = 3)
In vitro dissolution study

From the in vitro dissolution study it was found that AB-II formulation enhances the solubility of fexofenadine HCl better than other formulations. Comparison of dissolution profile of pure drug, physical mixtures and co ground mixtures was shown in fig. 4.

Fig. 4. Dissolution profile of (A) pure drug and various physical mixtures (± S.D. n =3), (B) pure drug and various co ground mixtures (3 hrs grinding) (± S.D. n =3), (C) pure drug and various co ground mixtures (6 hrs grinding) (± S.D. n =3), (D) Comparison

Pre compression parameters of powder blend

The results for all pre compression parameters including angle of repose 29.16 ±1.022, bulk density 0.45 ± 0.007 g/ml, tapped density 0.51 ± 0.006 g/ml, Carr’s index 13.19 ± 1.035 % and Hausner’s ratio 1.15 ± 0.021. Which indicate good flowability of powder blend.

Post-compression parameters of prepared MDTs

Results of post-compression parameters of prepared MDTs was shown in table IV
### Table IV Post compression parameters of prepared MDTs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Observation (± S.D. n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm)</td>
<td>3.21 ± 0.03</td>
</tr>
<tr>
<td>Weight Variation (mg)</td>
<td>102 ± 1.6</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>3.2 ± 0.91</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.58 ± 0.01</td>
</tr>
<tr>
<td><em>In vitro</em> disintegration time (sec)</td>
<td>27.31 ± 1.48</td>
</tr>
<tr>
<td>Wetting time (sec)</td>
<td>24 ± 1.67</td>
</tr>
<tr>
<td>Water absorption ratio (%)</td>
<td>77.37 ± 0.79</td>
</tr>
<tr>
<td><em>In vitro</em> dispersion time (sec)</td>
<td>33.36 ± 0.51</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>99.6 ± 0.77</td>
</tr>
</tbody>
</table>

**In vitro Dissolution test**

The MDT was allowed for *in vitro* drug release study in PBS (5% methanol) pH 6.8 as shown in fig. 5 (A). From *in vitro* drug release profile it was found that nearer 100% of drug release was occur within 16 min.

![Fig. 5. Dissolution profile of (A) optimized mouth dissolving tablet (n = 3), (B) MDT before and after stability study (after 1 month) (± S.D. n = 3)](image-url)

**Stability testing of drug (temperature dependent stability studies)**

Stability study was conducted at room temperature for one month storage. The tablets were withdrawn after a period of 30 days and analyzed for physical characterization such as visual defects, hardness, % friability, disintegration, % drug content and *in vitro* drug release profile. Table V depicts the tablet characteristics after stability study.
Table V Comparison of evaluation parameters of MDT before and after stability study

<table>
<thead>
<tr>
<th>Time duration</th>
<th>Parameters (± S.D. n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hardness (kg/cm²)</td>
</tr>
<tr>
<td>Initial</td>
<td>3.066 ± 0.12</td>
</tr>
<tr>
<td>After 1 month</td>
<td>3.07 ± 0.15</td>
</tr>
</tbody>
</table>

To check the similarity between two dissolution profile similarity factor $f_2$ was applied. The equation for $f_2$ is as below:

$$f_2 = 50 \log \left\{ 1 + \frac{1}{N} \sum wt(R_t - T_t)^2 \right\}^{0.5\times100}$$

Where, $R_t =$ amount of drug released before stability study  
$T_t =$ amount of drug released after stability study  
n = No. of experimental data  

Similarity factor $f_2$ was found to be 87.888.

**Contour plot and response surface plot**

The results obtained from experimental work were used to draw the contour plot and surface plot for each response variable such as average particle size ($Y_1$), saturation solubility ($Y_2$) and CPR in 5 min ($Y_3$) with the help of statistica software version 7 (fig. 6).

![Contour plot and surface plot](image)

Fig. 6. Contour plot and surface plot of (A) average particle size, (B) saturation solubility, (C) drug release in 5 min against D-mannitol, lactose and MCC (D) overlay contour plot of all variables.
DISCUSSION

The DSC curves of fexofenadine HCl revealed a single, sharp endothermic peak at 206 °C corresponding to the melting point (4). The DSC thermogram of co ground mixture (containing fexofenadine HCl, D-mannitol and lactose) shown the characteristic peaks corresponding to their respective melting point (fig. 1) which were same in drug and excipient mixture. Thus there was no any interaction between drug and excipients.

In the FTIR spectrum of fexofenadine HCl the characteristic peaks corresponding to aromatic C-H bending (648,667,695,701,744,776,854 cm\(^{-1}\)), carboxyl C=O stretching (1704 cm\(^{-1}\)), C-N stretching (1279 cm\(^{-1}\)), -OH group (3295 cm\(^{-1}\)) were identified, which were same in all drug and polymer mixtures. Thus there was no any interaction between drug and excipients.

All co ground mixtures were characterized for angle of repose, bulk density, tapped density, Carr’s compressibility index and Hausner’s ratio and they having satisfactory flow property. The drug content of all the co ground mixtures was within the range, co ground mixtures shown negligible change in drug content analysis.

**Particle size analysis**

When grinding time increases there was decrease in particle size. Particle size decreases in following manner → co ground mixtures for 6 hours grinding < co ground mixtures for 3 hours grinding < physical mixtures without grinding. A significant decrease in particle size was obtained in the case of AB-II co ground mixture. Comparison of average particle size of physical mixtures and co ground mixtures was shown in fig. 3

**Saturation solubility study**

Fexofenadine HCl has saturation solubility of 3.256 mg/ml. A significant increase in solubility was obtained in the case of AB-II co ground mixture; this may be due to the significance reduction in particle size.

**In vitro dissolution study**

From the *in vitro* dissolution study it was found that AB-II formulation enhances the solubility of fexofenadine HCl better than other formulations. All formulation showed increase in the solubility of drug with increase in grinding time with respect to pure drug.

The powder blend was characterized for angle of repose, bulk density, tapped density, Carr’s index and Hausner’s ratio and it having good flowability.

The MDTs having round shape, uniform size and thickness. The prepared MDTs pass the weight variation test and they having good hardness. The % friability was less than 1 % so they pass the friability test. The wetting time of MDTs was very less and having high water
absorption ratio, so they shown less disintegration time. The drug content of all the prepared MDTs was within the range, MDTs shown negligible change in drug content analysis.

**In vitro dissolution test for prepared MDTs**

From *in vitro* drug release profile it was found that nearer 100% of drug release was occur within 16 min. This faster release was achieved due to co-grinding. Co-grinding reduces the particle size and therefore there was increased in surface area of particles due to this there was enhancement of dissolution rate. Robust action of super disintegrant-crospovidone was also help for faster release.

**Stability testing of drug**

There was no any kind of visual defects seen on tablets. The hardness and % friability of tablets was within the range. Tablet passes from the disintegration parameter of MDT were selected for stability study. The drug content of all the tablets was within the range, selected tablets shown negligible change in drug content analysis and dissolution profile that can be inferred that tablets do not show any degradation of fexofenadine HCl with normal room temperature.

Similarity factor $f_2$ was found to be 87.888, which was in the range of 50-100. $f_2$ value indicated that the dissolution profiles before and after stability testing were almost similar and super imposable. This confirmed that prepared MDTs of fexofenadine HCl would be stable when packed in proper container.

**Contour plot and surface plot for average particle size ($Y_1$)**

The data demonstrate that $X_1$, $X_2$ and $X_3$ affect the average particle size. $X_3$ had great impact on average particle size. Here linear relationship was observed so if concentration of $X_3$ increases there was increased in average particle size. If concentration of $X_1$ and $X_2$ increases there was decreased in average particle size.

$$Y_1 = 6.65X_1 + 6.71X_2 + 8.39X_3 - 3.22X_1X_2 - 5.87X_2X_3 - 4.88X_1X_3 + 5.69X_1X_2X_3$$

**Contour plot and surface plot for saturation solubility ($Y_2$)**

The data demonstrate that $X_1$, $X_2$ and $X_3$ affect the saturation solubility. $X_1$ having great impact on $Y_2$ as compare to $X_2$ and $X_3$. There were linear relationship between $X_1$, $X_2$, $X_3$ and $Y_2$. If concentration of $X_1$, $X_2$ and $X_3$ increases there was increased in $Y_2$.

$$Y_2 = 5.42X_1 + 5.15X_2 + 4.76X_3 + 5.49X_1X_2 + 2.26X_2X_3 + 2.34X_1X_3 + 6.23X_1X_2X_3$$

**Contour plot and surface plot for drug release in 5 min ($Y_3$)**

The data demonstrate that $X_1$, $X_2$ and $X_3$ affect $Y_3$. $X_1$ having great impact on $Y_3$ as compare to $X_2$ and $X_3$. There were linear relationship between $X_1$, $X_2$, $X_3$ and $Y_3$. If concentration of $X_1$, $X_2$ and $X_3$ increases there was increased in $Y_3$. 
\[ Y_3 = 73.33X_1 + 71.66X_2 + 62.5X_3 + 53.36X_1X_2 + 34.32X_2X_3 + 38.36X_1X_3 + 83.17X_1X_2X_3 \]

**Overlay plot**

Overlay plot shows combine effect of all dependent variables on responses. In overlay plot there was an overlay region, this overlay region having some concentration ranges of \(X_1, X_2\) and \(X_3\), within these concentration ranges we get our desired responses \((Y_1, Y_2\) and \(Y_3\)).

**CONCLUSION**

When grinding time increased there was significant reduction in particle size observed and significantly saturation solubility was increased, due to these there was enhancement of dissolution rate observed. From this whole research work we can conclude that solubility of fexofenadine HCl was significantly enhanced by co grinding; thus the MDTs shown faster release of drug and prepared MDTs having good stability at room temperature.

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**REFERENCES**


