FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET CONTAINING QUETIAPINE FUMARATE
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ABSTRACT
Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablet. In the present work, fast dissolving tablets of quetiapine were prepared by direct compression method with a view to enhance patient compliance. Three super-disintegrants, viz., crospovidone, croscarmellose sodium and sodium starch glycolate in different ratios with microcrystalline cellulose along with directly compressible mannitol to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time and in vitro disintegration time. Based on in vitro disintegration time (between 57 to 75 s), the formulations were tested for the in vitro drug release pattern (in pH 6.8 phosphate buffer), and drug-excipients interaction (XRD).

Keywords: Fast dissolving tablets, quetiapine fumarate, crospovidone, Croscarmellose sodium, sodium starch glycolate

INTRODUCTION
Mouth dissolving drug delivery systems (MDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. MDDDS offer the luxury of much more accurate dosing than the primary alternative, oral liquids. This segment of formulation is especially designed for dysphagic, geriatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations. As they dissolve/disintegrate very fast when placed in the mouth, MDDDS are the most convenient dosage forms for dysphasic, paediatric and geriatric patients with swallowing problem. They do not require water for administration, thus are good alternative for travellers and for bed ridden patients.

Quetiapine fumarate, a dibenzothiazepine derivative, is an antipsychotic agent. Quetiapine and the active plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. The extent to which the N-desalkyl quetiapine metabolite contributes to the pharmacological activity of quetiapine is not known.

Quetiapine: Quetiapine exhibits affinity for brain serotonin 5HT2 and 5HT1A receptors, and dopamine D1 and D2 receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors, which is believed to contribute to the clinical antipsychotic properties and low extra pyramidal symptoms (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine also has high affinity for histamine H1 receptors and adrenergic α1 receptors, with a lower affinity for adrenergic α2 receptors, but no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors.1,7

N-desalkyl quetiapine
N-desalkyl quetiapine, similar to quetiapine, exhibits affinity for brain serotonin 5HT2 and dopamine D1 and D2 receptors. Additionally, like quetiapine, N-desalkyl quetiapine has high affinity at serotonin 5HT1 receptors, and histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors. Its insolubility in water and bland taste makes it an ideal candidate for fast disintegrating tablets with regards to palatability. Since epileptic patients have to strictly follow dosage regimen for preventing sub therapeutic concentration, MDT will avoid missing out of dose even during travelling or other situations where there is no access to water. The present investigation deals with the development of an effective and stable MDT of quetiapine having adequate hardness, low disintegration time and pleasant taste.

MATERIALS AND METHODS
Quetiapine fumarate was obtained from Ind-Swift limited, Microcrystalline cellulose, Starch, Crospovidone, Mannitol, Aspartame, Magnesium stearate, Talc were gifted from mankind pharmaceutical ltd.
ESTIMATION OF QUETIAPINE

An UV Spectrophotometric method based on the measurement of absorbance at 292nm, 0.1N HCl was used in the estimation of Quetiapine. The method obeyed Beer’s law in the concentration range of 5.5-55μg/ml. Low RSD values ensured reproducibility of the method. Thus the method was found to be suitable for the estimation of Quetiapine content in various products and in vitro dissolution studies.

PHASE SOLUBILITY STUDIES

Phase solubility measurements were performed according to the following method. An excess amount of drug complex was added to 10 mL 6.8 phosphate buffer solutions in volumetric flask and shaken on rotary flask shaker at constant temperature of 37 ± 0.5°C for 24 h. In order to reach equilibrium stands the solution for another 6 h. After equilibration the suspensions were filtered through 0.45 μm membrane filter and analyzed by UV11.

PREPARATION OF MIXED BLEND OF DRUG AND EXCIPIENTS

All the ingredients were passed through mesh No.60. Required quantity of each ingredient was taken from each specified formulation and all the ingredients were co ground in a mortar and pestle. The powder blend was evaluated for flow properties.

Data is given in table-1.

EVALUATION OF PRE-COMPRESSION PARAMETERS OF POWDER BLEND

Angle of Repose

Angle of repose was determined using funnel method9. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula:

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Bulk density:

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

\[ \rho_b = \frac{M}{V_b} \]

Tapped density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using the formula:

\[ \rho_t = \frac{M}{V_t} \]

Compressibility index: Compressibility index I is calculated as follows:

\[ I = \frac{V_0 - V_t}{V_0} \times 100 \]

V0 is the bulk volume
Vt is the tapped volume.

The value below 15%indicates a powder with usually give rise to good flow characteristics where as above 25% indicate poor flowability.

Haussner’s ratio: Haussner’s ratio is an indirect index of ease of powder flow. It is calculated by the following formula:

Haussner’s ratio = pt/ρb

pt = tapped density

ρb = bulk density

Lower Haussner’s ratio (<1.25) indicates better flow properties than higher ones (>1.25)

Data is given in table -2

PREPARATION OF TABLETS

Fast dispersible tablets containing 25mg of Quetiapine fumarate were prepared by direct compression method and the various formula used in the study are shown in Table 1.

All the ingredients without magnesium stearate and talc were mixed uniformly followed by addition of magnesium stearate and talc. Super disintegrants like sodium starch glycolate, crosspovidone and crosscarmellose sodium were used in different ratios and finally the effects of combination of super disintegrants were studied. After evaluation of powder blend tablets were compressed with single station tablet punching machine using 8 mm flat punches set.

EVALUATION OF TABLETS

Uniformity of weight (Weight Variation)17

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Data is given in table -4

Hardness18

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was determined using a Monsanto hardness tester.

Friability18

Friability of tablets was measured by using Roche Friabilator (Electrolab, Mumbai, India). Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered acceptable.

In-vitro disintegration time18

The disintegration time was measured using a USP paddle method. The tablets were dropped in each six tubes of apparatus and one disk was added to each of them. The vessel was filled with 500 ml of water maintained at 37 °C. The paddle was rotated at 100 revolutions per minute. The tablet was placed inside the sinker and the time at which it passes completely through the mesh of sinker was taken as the disintegration of the tablet.

Wetting time18

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

Drug content estimation19

Twenty tablets were weighed and powdered. An amount of powder equivalent to 25 mg of Quetiapine fumarate was dissolved in 100ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 254 nm using UV-Visible spectrophotometer19.

Thickness18

The thickness of tablets was determined by using vernier caliper18.

Data is given in Table -3

Dissolution study18

The dissolution study was performed for pure drug formulation and batches F1-F9 by using USP II paddle type dissolution apparatus. The dissolution medium was phosphate buffer pH 6.8 (900 mL, 37 ± 0.50°C). The rate of agitation of the paddle was 50 rpm. Aliquot of dissolution medium was withdrawn at specific time interval of 2 minutes,
it was filtered and absorbance was measured spectrophotometrically at 290 nm by UV spectrophotometer. Graph is shown in figure-1

**DRUG CHARACTERIZATION**

**Infrared spectroscopy study**

The study was carried out to determine the molecular structure serving as an identification test to ascertain the purity of the molecule. IR spectroscopy was obtained by a FTIR spectrophotometer (Shimadzu, Japan) using NaCl pellets and scanning range used was 4000 to 400 cm-1 at a scan period of 1 min. Spectra of pure drug is done. There is no change in the shape of the peak or shift of the peak as compare to standard.

FTIR is given in figure- 6

**X-Ray Diffraction Study**

The XRD patterns of drug powder and different mixtures of drug with superdisintegrant were recorded. X-ray diffraction patterns of Quetiapine fumarate revealed highly crystalline nature. The XRD Spectra of above formulation shows no significant changes in peaks. Hence it concluded that the excipients were compatible with each other.

XRD is given in figure-2 to 5

**RESULTS AND DISCUSSION**

In the present investigation FDTs of Quetiapine fumarate were prepared by direct compression method. Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. Values for angle of repose were found in the range of 25.63 to 36.81°. Carr’s index of the prepared blends falls in the range of 12.0 to 22.554% and this is also supported by Hausner factor values which were in the range of 1.16 to 1.2. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture.

All the tablets were prepared under similar conditions. All the formulations exhibited white colour, odourless with smooth surface. The average weight of the FDTs prepared by direct compression method was 200.00 to 214.00 mg. Weight variation of FDTs was within limits. Hardness and friability of all formulations were within acceptable limits. Hardness of tablets prepared by direct compression was 3.85 to 4.56 kg/cm2. The friability of all formulations was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping. Disintegration time is very important for FDTs which is desired to be less than 60 seconds for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of prepared FDTs was in the range of 57 to 75 seconds and the order was Crospovidone < croscarmellose sodium < SSG. As the concentration of superdisintegrants in the formulations increased the disintegration time was found to decrease. Wetting time is used as an indicator from the ease of the tablet disintegration in buccal cavity. It was observed that wetting time of tablets was in the range of 40 to 52 seconds. It was observed that type of the disintegrant affected the wetting of the tablets. On comparing superdisintegrants the formulation containing SSG take more wetting time than croscarmellose sodium and Crospovidone. The percentage drug content of the prepared tablets was in the range of 97.8 to 99.5. mg per tablet. In vitro dissolution studies of the prepared FDTs was performed in artificial saliva (pH 6.8) using USP dissolution apparatus type 2. It was observed that as the concentration of superdisinterggrant increased the drug release also increased. With reference to the type of superdisintegrant, the release rate was found to follow the order: Crospovidone > Ac-Di-sol > SSG.

**CONCLUSION**

The phase solubility studies of Quetiapine fumarate shows that it has a pH-dependent solubility and shows more solubility in 0.1N HCl and as the pH is increased the solubility get decreased. Analysis of dissolution data showed an increase in dissolution rate with superdisintegrant crospovidone in comparison to croscarmellose sodium and sodium starch glycolate. Formulation with higher concentration of Crospovidone (t) has satisfactory physical resistance, fast in vitro disintegration time, high dissolution rate. Rapid disintegration of tablets formulated in this investigation may possibly help in administration of Quetiapine fumarate in a more palatable form without water. Thus, the dosage form of various drugs, especially for pediatric, geriatric, bed ridden, and non-cooperative patients, can be successfully formulated using this technology.

**REFERENCES**


### Table-1 FORMULA USED FOR THE PREPARATION OF TABLETS

<table>
<thead>
<tr>
<th>Formulation ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<td>Crospovidone (mg)</td>
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<td>Croscarmellose (mg)</td>
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<td>-</td>
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<td>SSGi (mg)</td>
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<td>MCC (mg)</td>
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<td>Talc (mg)</td>
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<td>Mannitol (mg)</td>
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### Table-2 PRECOMPRESSION PARAMETERS

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<th>F7</th>
<th>F8</th>
<th>F9</th>
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<tbody>
<tr>
<td>Bulk density Gm/cm³</td>
<td>0.448±0.03</td>
<td>0.440±0.02</td>
<td>0.449±0.004</td>
<td>0.519±0.02</td>
<td>0.520±0.04</td>
<td>0.550±0.03</td>
<td>0.529±0.05</td>
<td>0.525±0.03</td>
<td>0.528±0.02</td>
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<tr>
<td>Tapped density Gm/cm³</td>
<td>0.559±0.05</td>
<td>0.560±0.02</td>
<td>0.612±0.04</td>
<td>0.607±0.03</td>
<td>0.524±0.04</td>
<td>0.510±0.02</td>
<td>0.611±0.02</td>
<td>0.614±0.03</td>
<td>0.620±0.02</td>
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<td>Angle of repose (Degree)</td>
<td>25.663±0.8</td>
<td>26.229±0.77</td>
<td>28.307±1.61</td>
<td>30.452±1.38</td>
<td>32.113±1.37</td>
<td>33.804±1.2</td>
<td>30.781±0.77</td>
<td>33.804±1.22</td>
<td>36.811±0.90</td>
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<tr>
<td>compressibility %</td>
<td>26.931±0.246</td>
<td>08.536±1.981</td>
<td>15.871±1.922</td>
<td>14.144±1.156</td>
<td>14.394±0.535</td>
<td>12.284±0.314</td>
<td>18.107±0.556</td>
<td>15.431±0.588</td>
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<td>HAUSNER'S ratio %</td>
<td>1.2</td>
<td>1.16</td>
<td>1.17</td>
<td>1.16</td>
<td>1.2</td>
<td>1.19</td>
<td>1.16</td>
<td>1.2</td>
<td>1.18</td>
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<td>Carr's index</td>
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<td>13.367±2.343</td>
<td>14.906±2.682</td>
<td>16.488±1.561</td>
<td>16.818±0.731</td>
<td>14.005±0.408</td>
<td>18.12±0.659</td>
<td>15.74±0.657</td>
<td>22.38±1.119</td>
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### Table-3 POST COMPRESSION DATA

<table>
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<tr>
<th>Formulation</th>
<th>Thickness(mm) n=3</th>
<th>Hardness (kg/cm²) n=3</th>
<th>Diameter (mm) N=3</th>
<th>Friability %</th>
<th>Drug content %</th>
<th>Disintegration sec</th>
<th>Wetting time sec</th>
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<tbody>
<tr>
<td>F1</td>
<td>3.1±0.02</td>
<td>4.4±0.25</td>
<td>8.0±0.01</td>
<td>0.451</td>
<td>99.2±0.88</td>
<td>57±2</td>
<td>43±4</td>
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<td>F2</td>
<td>3.12±0.02</td>
<td>4.56±0.31</td>
<td>8.02±0.02</td>
<td>0.57</td>
<td>99.0±0.92</td>
<td>55±3</td>
<td>40±3</td>
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<td>F3</td>
<td>3.14±0.01</td>
<td>3.92±0.17</td>
<td>8.01±0.01</td>
<td>0.486</td>
<td>99.5±0.95</td>
<td>55±4</td>
<td>42±2</td>
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<td>F4</td>
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<td>4.2±0.28</td>
<td>8.02±0.02</td>
<td>0.752</td>
<td>98±1.02</td>
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<td>F5</td>
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<td>8.03±0.03</td>
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<td>98.2±1.3</td>
<td>65±4</td>
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<td>F7</td>
<td>3.11±0.01</td>
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<td>F8</td>
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<td>69±4</td>
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<td>F9</td>
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### Table-4 WEIGHT VARIATION DATA

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<td>F2</td>
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<td>F9</td>
<td>201.85±1.66</td>
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FIGURE 1 DISSOLUTION DATA GRAPH (pH 6.8)

FIGURE 2 PURE DRUG QUETIAPINE FUMARATE

FIGURE 3 QUETIAPINE FUMARATE + CROSCARMELOSE SODIUM

FIGURE 4 QUETIAPINE FUMARATE + CROSSPOVIDONE
Source of support: Nil, Conflict of interest: None Declared