A STUDY ON SUPERDISINTEGRANTS: IN THE FORMULATION OF TIZANIDINE HYDROCHLORIDE ORAL DISSOLVING TABLETS

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ABSTRACT
Tizanidine is a short acting muscle relaxant drug. Tizanidine hydrochloride is a central adrenergic agonist acts by inhibiting the excitatory amino acids release in spinal interneurons. Fast dissolving tablets are disintegrating or dissolving rapidly in the saliva without the need of water and are designed to dissolve in saliva remarkably fast, within a few seconds. The current study aimed to formulate fast dissolving tablets of Tizanidine hydrochloride using, super disintegrants such as Kyron T-314, Crospovidone and Emcosoy. Formulated tablets were involved to evaluate hardness test, weight variation test, thickness test, friability test, drug content, wetting time, water absorption ratio, In vitro release studies. The results were found satisfactory as per the specified in monographs. The study report reveals that formulation CP3 (Crospovidone based formulation) and formulation KY3 (Kyron T-314 based formulation) showed highest release rate, 98.10% and 96.17% respectively within 5 min. Moreover, it suggests, fast dissolving tablets will be a promising delivery system to improve therapeutics efficacy of Tizanidine.

KEYWORDS
Fast dissolving tablets, Tizanidine HCL, Emcosoy, Crospovidone and Kyron T-314.

INTRODUCTION
Oral drug delivery systems are wide accepted and most preferable (50-60%) route of administration for many drugs due to its several benefits. In the modern era, among various oral drug delivery systems, fast dissolving tablets are most preferable one. Hence, fast dissolving tablets are also called as mouth dissolving tablets, melt in mouth tablets, oro-dispersible tablet, rapid melts, porous tablets, quick dissolving tablets etc1. U.S Food and Drug Administration (USFDA) defined orally fast dissolving tablets are “a solid unit
dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a few seconds when placed upon the tongue”. The disintegration time for orally disintegrating tablets generally ranges from few seconds to about a minute\(^2,3\). Tizanidine hydrochloride is an imidazoline derivative used for muscle relaxant, which acts as agonist on \(\alpha_2\) receptor (centrally) and leads to myotonolytic effects on skeletal muscle. Bioavailability of Tizanidine is about 34-40\(^%\)\(^4,5\).

**MATERIAL AND METHODS**

Tizanidine HCL (gift sample) was obtained from Symed Labs Ltd., Hyderabad, India. Emcosoy was obtained from JRS Pharma Gmbh and Co. KG, Germany. Kyron T-314 was obtained from Corel Pharma Chem. Ahmedabad, India. Crospovidone, Microcrystalline cellulose, Mannitol, Talc, Magnesium stearate was purchased from S.D. Fine Chem. Ltd., Mumbai, India. Sucralose Merck Chem. Ltd., Mumbai, India. Orange flavor was obtained from Leo chem. Ltd., Bangalore, India. The powder blend for compression of fast dissolving tablet were prepared initially by weighing drug and other excipients except magnesium stearate (mentioned in Table No.1) and then mixed in an ascending order of their weight for at least 15 mins. After blending of above mixture is added with magnesium stearate and mix for 5 minutes\(^6\). Finally, the powder blend (100mg) was directly compressed using 6mm, round shaped tablet compression machine (Riddhi machinery Ltd., India).

**FTIR spectroscopy**

FTIR spectroscopy is a technique mostly used in formulation to determine the functional groups level interaction and it was performed on Fourier transform infrared spectroscopy (Shimadzu 8400S). Spectra for pure drug, physical mixture of drug with different polymers were obtained by scanning over the range of 4000-400 cm\(^{-1}\)using KBr pellet technique\(^7,8\) and shown in the Figure No.1.

**Pre-compression properties**

The prepared blend mixture of each formulation were involved to determine the pre-compression parameters such as bulk density, tapped density, angle of repose, Carr’s index, Hausner’s ratio. The results were reported as the mean (±) standard deviation of three measurements as mentioned in Table No.2.

**Bulk density (\(D_b\)), Tapped density (\(D_t\)) and Hausner’s ratio**

10 gm of powder was introduced into dried and clean 100ml measuring cylinder, at a constant height the cylinder was tapped for 100 times and the tapped volume was read in the case of tapped density determination. But the bulk density was determined from the bulk volume and Hausner’s ratio was calculated by using the below mentioned formulas\(^9\).

\[
D_b = \frac{M}{V_o}
\]

Where, \(D_b\) = Bulk density (gm/cc)

\[
M = \text{mass of the powder (g)}
\]

\[
V_o = \text{bulk volume of powder (cc)}
\]

\[
D_t = \frac{M}{V_o}
\]

Where, \(D_t\) = Tapped density (gm/cc)

\[
M = \text{mass of the powder (g)}
\]

\[
V_o = \text{bulk volume of powder (cc)}
\]

Hausner's ratio = Tapped density/Bulk density

**Compressibility index**

After the determination of tapped (TBD) and bulk density (LBD), the compressibility of powder was determined by the Carr's compressibility index using given formula\(^10\).

\[
\text{Carr's index (\%) = } \frac{[(\text{TBD-LBD}) \times 100]}{\text{TBD}}
\]

**Angle of repose**

Angle of repose of the granules was determined by height cone method. A funnel was fixed to a desirable height and granules were filled in it. Thus the granules were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using below mentioned formula\(^11\).

\[
\Theta = \tan^{-1}(\frac{h}{r})
\]

Where, \(\Theta\) = angle of repose

\(h\) = height of pile

\(r\) = radius of the base of the pile

**Evaluation of compressed tablet**

The prepared floating tablets were evaluated for their hardness, friability, thickness, weight variation, wetting time and absorption ratio, disintegration time, drug content. The values were mentioned in Table No.3.

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Weight variation
20 tablets of each formulation were weighed using electronic balance and the test was performed according to official method\textsuperscript{12,13}. The IP limit for weight variation in case of tablet weight between the range 80 to 250 mg is ±7.5%.

Thickness
The thickness of 10 tablets from each formulation was measured using Vernier calipers. The extent to which the thickness of each tablet deviated from ±5% of the standard value was determined\textsuperscript{14}.

Hardness and Friability
Friability means the condition of being friable, describes the tendency of a solid substance to break in to smaller pieces under duress or contact. About 20 tablets were weighed together and then placed in Roche friabilator chamber, (Electro lab, India). The friabilator was operated for 100 revolutions so that, the chamber carrying the tablets drops them at a distance of 6 inches with every revolution. Because during revolution, the tablet were subjected to combined effects of abrasion and shock. Then the tablets were dusted and re-weighed to determine the friability\textsuperscript{15}.

Wetting time and absorption ratio
A piece of tissue paper folded twice was placed in a small petridish containing 6ml of simulated saliva pH 6.8. Tablet was placed on a paper and time required for complete wetting was measured. Water absorption ratio(R), was determined using following equation.
\[
R = 100\frac{(W_a-W_b)}{W_b}
\]
Where, \(W_b\) - weight of tablet before absorption
\(W_a\) - weight of tablet after absorption

Three tablets from each formulation were tested. Average and standard deviation was determined and reported at Figure No.2.

Uniformity of drug content
Ten tablets from each batch were weighed accurately and powdered. An amount of powder equivalent to 6mg of the drug was transferred into a 25ml volumetric flask. The volume was made with 6.8 pH phosphate buffer and sonicated for 10 min. The resulting solution was filtered and assayed at 228 nm using UV spectrophotometer (1800, Shimadzu, Kyoto, Japan)\textsuperscript{16}.

Disintegration test
The disintegration test was carried out using disintegration test apparatus (Electro lab, India) Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled water was used as a medium maintained at 37°C ± 0.5°C and the time taken for each tablet to disintegrate completely was recorded\textsuperscript{17}.

In vitro release and release kinetic studies
Drug release study was carried out using USP type II dissolution test apparatus (Electro lab, India).The dissolution medium used was 900 ml of 6.8 pH buffer at 37°C ±0.5°C. The paddle speed was kept at 50 rpm throughout the study. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a sink condition. Each sampling was analyzed spectrophotometrically at 228 nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan). The \textit{In vitro} drug release profile data for Tizanidine fast dissolving tablets was mentioned in Table No.4. Graphs were plotted between % CDR and time for all the formulations and shown in the FigureNo.3, 4, 5\textsuperscript{18}. The data of the \textit{In vitro} release studies were plotted in different kinetic models to study the release behavior and were shown in Figure No.3-5\textsuperscript{19}.

RESULTS AND DISCUSSION
FTIR spectra for all the formulations showed similar absorption bands as their respective physical mixtures with drugs. Result suggested that there was no chemical interaction between drug and superdisintegrants. Studies for various physicochemical characterizations include pre-compression parameters report shows all the formulations were in the specific range. Post-compression parameters such as weight variation was within the pharmacopoeial limit and thickness were found to be within the range of 2.96-3.03mm. The hardness and friability of prepared fast dissolving tablet were found to be 2.83 to 3.46 kg/cm\textsuperscript{2} and 0.261 to 0.766% respectively. Wetting time and absorption ratio of the tablet were in the range of 97 to 128.7%. Drug content of prepared tablet were reported in the...
The % CDR of prepared tablets was reported in Table No.5. From the drug release and drug kinetic studies of TIZ formulations were found to be fairly linear (kinetics data not mentioned here).

Table No.1: Formulation of Tizanidine FDTs with different super disintegrants (KY-Kyron, CP-Crospovidone, EM-Emcosoy)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients (mg)</th>
<th>KY1</th>
<th>KY2</th>
<th>KY3</th>
<th>CP1</th>
<th>CP2</th>
<th>CP3</th>
<th>EM1</th>
<th>EM2</th>
<th>EM3</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>Micro crystalline cellulose</td>
<td>61</td>
<td>60</td>
<td>60</td>
<td>61</td>
<td>60</td>
<td>60</td>
<td>61</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Kyron T-314</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Crospovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Emcosoy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Sucralose</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<td>8</td>
<td>Magnesium stearate</td>
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<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>9</td>
<td>Talc</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</table>

Pre-compression parameters data

Table No.2: Pre-compression parameters of developed formulations

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation Code</th>
<th>Angle of repose (θ)</th>
<th>Bulk density (g/cc)</th>
<th>Tapped density (g/cc)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KY1</td>
<td>27.61±0.68</td>
<td>0.371±0.005</td>
<td>0.421±0.01</td>
<td>11.87</td>
<td>1.13</td>
</tr>
<tr>
<td>2</td>
<td>KY2</td>
<td>28.94±0.91</td>
<td>0.353±0.002</td>
<td>0.409±0.006</td>
<td>13.69</td>
<td>1.15</td>
</tr>
<tr>
<td>3</td>
<td>KY3</td>
<td>27.76±0.51</td>
<td>0.342±0.005</td>
<td>0.398±0.007</td>
<td>14.07</td>
<td>1.16</td>
</tr>
<tr>
<td>4</td>
<td>CP1</td>
<td>28.36±0.44</td>
<td>0.378±0.005</td>
<td>0.420±0.004</td>
<td>10</td>
<td>1.11</td>
</tr>
<tr>
<td>5</td>
<td>CP2</td>
<td>30.25±0.65</td>
<td>0.386±0.003</td>
<td>0.459±0.000</td>
<td>15.9</td>
<td>1.18</td>
</tr>
<tr>
<td>6</td>
<td>CP3</td>
<td>30.67±0.49</td>
<td>0.386±0.006</td>
<td>0.448±0.004</td>
<td>13.83</td>
<td>1.16</td>
</tr>
<tr>
<td>7</td>
<td>EM1</td>
<td>26.92±0.31</td>
<td>0.353±0.002</td>
<td>0.409±0.006</td>
<td>13.69</td>
<td>1.15</td>
</tr>
<tr>
<td>8</td>
<td>EM2</td>
<td>27.01±0.45</td>
<td>0.358±0.005</td>
<td>0.416±0.007</td>
<td>13.94</td>
<td>1.16</td>
</tr>
<tr>
<td>9</td>
<td>EM3</td>
<td>29.53±0.66</td>
<td>0.368±0.009</td>
<td>0.433±0.004</td>
<td>15.04</td>
<td>1.17</td>
</tr>
</tbody>
</table>
## Post-compression parameters data

**Table No.3: Post compression Parameter of developed Formulations**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Form. Code</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)*</th>
<th>Weight variation (mg)*</th>
<th>Wetting Time (sec)</th>
<th>Water abs. ratio (%)</th>
<th>Disintegration time (sec)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KY1</td>
<td>3.01±0.02</td>
<td>2.90±0.17</td>
<td>0.671</td>
<td>99.45±1.43</td>
<td>107.0±1.66</td>
<td>101.7±1.03</td>
<td>67.6±1.15</td>
<td>99.5±0.53</td>
</tr>
<tr>
<td>2</td>
<td>KY2</td>
<td>2.96±0.01</td>
<td>2.83±0.05</td>
<td>0.766</td>
<td>99.35±1.63</td>
<td>101.0±1.55</td>
<td>97.0±0.89</td>
<td>55.6±0.47</td>
<td>98.8±0.69</td>
</tr>
<tr>
<td>3</td>
<td>KY3</td>
<td>3.03±0.05</td>
<td>2.96±0.11</td>
<td>0.412</td>
<td>99.90±1.33</td>
<td>88.7±1.42</td>
<td>121.9±1.47</td>
<td>33.2±0.94</td>
<td>98.2±0.15</td>
</tr>
<tr>
<td>4</td>
<td>CP1</td>
<td>3.00±0.02</td>
<td>3.23±0.05</td>
<td>0.261</td>
<td>100±0.85</td>
<td>79.5±1.54</td>
<td>122.6±0.74</td>
<td>30.3±2.51</td>
<td>99.3±0.77</td>
</tr>
<tr>
<td>5</td>
<td>CP2</td>
<td>3.02±0.06</td>
<td>3.36±0.15</td>
<td>0.672</td>
<td>100.1±0.85</td>
<td>60.6±0.89</td>
<td>110.1±1.90</td>
<td>18.6±0.57</td>
<td>99.3±0.98</td>
</tr>
<tr>
<td>6</td>
<td>CP3</td>
<td>2.99±0.01</td>
<td>3.40±0.17</td>
<td>0.724</td>
<td>99.85±0.98</td>
<td>40.2±1.24</td>
<td>103.8±0.55</td>
<td>15.6±1.52</td>
<td>98.1±1.38</td>
</tr>
<tr>
<td>7</td>
<td>EM1</td>
<td>2.99±0.01</td>
<td>3.46±0.05</td>
<td>0.263</td>
<td>99.95±0.88</td>
<td>221.3±0.88</td>
<td>109.1±0.61</td>
<td>109.5±0.88</td>
<td>99.5±1.48</td>
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<tr>
<td>8</td>
<td>EM2</td>
<td>3.02±0.06</td>
<td>3.40±0.10</td>
<td>0.419</td>
<td>100±0.79</td>
<td>183.4±1.62</td>
<td>128.7±0.43</td>
<td>58.8±1.06</td>
<td>99.1±0.54</td>
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<tr>
<td>9</td>
<td>EM3</td>
<td>3.01±0.01</td>
<td>3.43±0.11</td>
<td>0.318</td>
<td>100±0.79</td>
<td>130.1±0.34</td>
<td>111.2±1.84</td>
<td>78.9±1.11</td>
<td>98.6±0.82</td>
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</table>

## Wetting time and absorption ratio of TIZ FDT’s

**In vitro drug release data**

**Table No.4: In vitro dissolution profile data of formulations**

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>% Cumulative Drug Released</th>
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<tr>
<td></td>
<td>KY1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>36.37±0.55</td>
</tr>
<tr>
<td>3</td>
<td>60.45±0.63</td>
</tr>
<tr>
<td>5</td>
<td>81.86±0.75</td>
</tr>
<tr>
<td>7</td>
<td>90.10±1.10</td>
</tr>
<tr>
<td>9</td>
<td>98.39±0.55</td>
</tr>
<tr>
<td>11</td>
<td>--</td>
</tr>
</tbody>
</table>
Figure No.1: FTIR spectra of (a) Tizanidine hydrochloride, (b) Kyron T-314, (c) Crospovidone, (d) Emcosoy, (e) physical mixture of TIZ, KY and CP, (d) physical mixture of TIZ and EM

(A) Initial wetted tablets
Figure No.2: (A) Initial wetting time and absorption ratio a) KY1-based tablet b) KY2-based tablet c) KY3-based tablet d) CP1-based tablet f) CP3-based tablet g) EM1-based tablet h) EM2-based tablet i) EM3-based tablet. (B) Completely wetting time and absorption ratio a) KY1-based tablet b) KY2-based tablet c) KY3-based tablet d) CP1-based tablet e) CP2-based tablet f) CP3-based tablet g) EM1-based tablet h) EM2-based tablet i) EM3-based tablet

Figure No.3: Dissolution profile of Tizanidine FDTs with KYRON T-314

Figure No.4: Dissolution profile of Tizanidine FDTs with Crospovidone
CONCLUSION
From the various pre and post compression data shows that presence of superdisintegrants in the fast dissolving tablets are remarkable. Moreover, the FTIR report proves the compatibility of superdisintegrants with drug. Among the various formulations the superdisintegrants like Crospovidone and Kyron based formulations were fasten the drug release in short duration (within 5 mins). From this study it’s concluded that addition of superdisintegrants will be a right choice for the formulations of Tizanidine fast dissolving tablets.

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CONFLICT OF INTEREST
We declare that we have no conflict of interest.

BIBLIOGRAPHY


