Simple Artificial Oral Cavity Model for *in vitro* Evaluation of Orally Disintegrating Tablets

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**Keywords:** artificial oral cavity, orodispersible dosage form, disintegration test, MG apparatus

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**Abstract**

Many patients who have problems in swallowing of solid dosage forms may benefit the Orodispersible tablets, where they rapidly disintegrate and dissolve in the oral cavity. Yet, there is no official and reproducible in vitro test that can predict the disintegration time. The present study was designed to evaluate a novel in vitro model for evaluation of disintegration time of the orodispersible tablets. A novel simple apparatus was prepared to simulate the oral cavity known as MG apparatus; it consists mainly of adult dental set with saliva input reservoir and digital monitoring. To validate the MG apparatus, nine blank orodispersible tablets were prepared using different concentrations of four superdisintegrants, in addition one of them prepared under different compression forces as well as subjected to stress storage condition (50°C/75%RH for 2 weeks). Also, five commercial orodispersible tablets were used to compare between the saliva and buffer as disintegration media. Moreover, sixteen volunteers were participated in human sensory tests for disintegration. The results indicate that there is a very high correlation between the novel *in vitro* disintegration test using the new method (MG apparatus) and the *in vivo* disintegration using human sensory test; while poor correlation was reported with the conventional method. In conclusion, the novel MG method is simple and highly correlated with the *in vitro* method and might be of value to predict disintegration time for orodispersible solid dosage forms.

** التطوير تجويف فموي صناعي يستخدم لتقدير الوقت délai لتفتت الحبوب التي تتفت سريعا في الفم مختبريا**

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**المفتاح البحث:** تجويف فموي صناعي، أشكال دوائية تتفتت في الفم، اختبار التفتت، جهاز MG

**المشخص**

كثير من المرضى ومنهم كبار السن والأطفال لديهم صعوبة في بلع الأدوية وخاصة الصباغة منها. إن ذلك فان المستحث الذي يفتت سريعا في الفم هو حل لهذه المشكلة.

الحبوب التي تتفتت في الفم هي تقنية مبتكرة تتيح تدفقها بالعاجل عند وضع فوق اللسان بدون الحاجة للماء.

بالرغم من أن وقت التفتت يعتبر معيار رئيسي لتقييم أداء الحبوب السريعة التفتت، لكن لحد الآن لا يوجد طرق دستورية بسيطة ودقيقة في المختبر وذلك لأن حجم اللعاب قليل ولذلك سرعة تفتت الحبوب.
Introduction

Recently, the oral disintegration tablets (ODT) are highly interested by pharmaceutical researchers because of their advantages over the conventional oral solid dosage forms like tablets, capsules, pills, granules, and powders regarding patient compliance, convenience, and performance which consequently produce efficient therapy [1-5]. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue” [6]. Additionally, the European Pharmacopoeia describes orodispersible tablet as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing [7]. The main critical property of ODTs is the disintegration time in the buccal cavity over the tongue; but there is no official test specific for ODTs reported until now. Although many trials to do the disintegration test have been published by many researchers including the use of CCD camera, Texture Analyzer, and modified dissolution apparatus [8-11], however, they are either complicated or not reproducible. Also in most of published articles the conventional disintegration tests for normal tablets described in the Pharmacopoeias are used for ODTs, but the results are widely variable due to the large test volume of disintegration medium used compared to normal saliva volume which is not more than few milliliters [12]. This may lead to alternative use of an in vivo study that depends on human sensation which has many difficulties especially when the drug is pharmacologically potent. To overcome these problems, a novel simple apparatus that simulate the adult human oral cavity has been developed to provide the same saliva flow rate at 37°C with digital monitoring to a video that record the disintegration process. To evaluate the new apparatus (MG), nine formulas of blank ODTs were prepared with different types and concentrations of super-disintegrants by direct compression method. Also the selected formula was prepared under three compression forces and subject to stress storage condition. As well as five commercial marketed tablets of different weights, sizes, and shapes were used in evaluation. The purpose of this study was to develop simple, applicable, and highly reproducible in vitro disintegration test for ODTs with in vivo results.

Materials and Methods

Materials

Cab-O-Sil and Mannitol were purchased from (Sigma-Aldrich, Germany). Talc, HCl, and Mg stearate were purchased from (BDH, England). Sodium starch glycolate (SSG), Cross-povidone (CP), and Cross-carmellose sodium were purchased from (Loba chemical, India). Calcium Chloride was purchased from (Gainland Chemical Company, U.K). Sodium Bicarbonate was purchased from (Teen Tech. Northants, U.K). Disodium hydrogen orthophosphate was purchased from (Sharlauchemie, EU). All other chemicals used in the study were of analytical grade. The commercial ODTs used in this study were purchased from the local market include Oronime® tablets, (TAD Pharma Italia S.r.l.); OlenazRapitab®, (Sun Pharmaceutical Ltd., India); Domstal-5 DT® tablets, (Torrent...
Preparation of blank ODTs

The ODT formulations utilized in the present study (Table 1) were prepared using super-disintegrants (SSG, CCS, Crospovidone, and MCC), mannitol as a diluent, with cab-o-sil, talc, and magnesium stearate as a flow promoters. They were mixed together in geometrical order for 10 min, and passed through sieve no. 18. The powdered mixture was then blended for 2 min with cab-o-sil, talc, and magnesium stearate and then compressed directly into tablets using 8 mm single punch tablet machine (Manesty Type F, Liverpool, England).

Evaluation of the prepared ODTs

Thickness.
Ten tablets from each formula were selected randomly and their thickness was measured with a micrometer screw gauge [13].

Hardness.
The crushing strength of the tablets was measured using a Monsanto hardness tester and expressed as a force in kg/cm² required for crushing the tablet. Six tablets from each formula batch were tested randomly and the average reading ± SD was recorded [14].

Friability.
Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was calculated using the following equation [13].

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

Conventional in vitro Disintegration Test

The in vitro disintegration tests were done for ODTs according to the British Pharmacopeia at 37±0.5°C using artificial saliva as a disintegration medium. Disintegration apparatus with a basket rack assembly containing six open ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time required for complete disintegration of the tablets, with no palpable mass remaining in the apparatus, was measured visually using a stopwatch, the mean of six readings were reported [15]. The artificial saliva solution was prepared according to the method proposed by Mariano et al (Table 2) [16].

Measurement of disintegration time by human sensory test

The disintegration time of ODTs was measured in sixteen healthy male volunteers (22–37 years old). The disintegration test in the oral cavity was assessed according to the method described by Ogata et al [17].

The volunteers were informed about the protocol and purpose of the study; all were asked to rinse their oral cavity with water prior to the test. Each volunteer was asked to place one tablet on the tongue and close the mouth; a stopwatch was started immediately. The end point of disintegration in the human sensory test was defined as the time when the tablet placed on the tongue had disintegrated without leaving any lumps. All the volunteers were instructed to rinse their mouth after completion of the test. This study was performed in accordance with the regulations of the Declaration of Helsinki about research in humans [18].

The Novel disintegration method (The MG-Model)

The MG apparatus consists mainly from 3 parts; the disintegration medium reservoir, the simulated oral cavity, and digital monitoring system as shown in figure (1). The reservoir contains heater with thermostat to control the temperature of disintegration medium; the liquid was transferred through a tube at controlled flow rate by valve to enter into the oral cavity around the tongue from multiple small
orifices in the tube. The simulated oral cavity, which is an adult dental set of lower and upper jaws, was connected by screw and instilled in a container with drainage tube to control the level of fluid in the cavity. The tongue was replaced by porous sponge filled the lower jaw around it. A tube with multiple orifices was supplied with fluid at controlled rate as shown in figure (2). The digital monitoring system consists of dental mini-camera (USB mini microscope A002 Adjustable auto-focus microscope; Shenzhen Kingsen Technology Co., Ltd. China) connected to a computer for recording the disintegration process as video images. In this MG-model (or the MG method), the temperature of disintegration medium in the reservoir was controlled at 37±0.5°C and start to flow at 1.0 ml/min for 10 min to ensure that the liquid reach the tongue; then the disintegration test can be initiated by putting the tablet over the tongue and close the upper jaw while the camera record the processes until the disintegration is complete.

**Effect of concentration and type of superdisintegrant**

Nine blank formulas were prepared (F1-F9) using different concentrations (2.5, 5, and 10%) and types of superdisintegrants (CCS, SSG, CP, and MCC) to study their effect on hardness and disintegration time.

**Effect of force of compression**

The selected formula was prepared under different compression forces (25, 30, and 35 KN) to study the effect of compression force on hardness and disintegration time.

**Effect of stress storage condition**

Stability studies were carried out for the ODTs; the tablets were stored at 50 °C/75 ± 5% RH using saturated sodium chloride solution desiccator for two weeks. After storage, samples were withdrawn and tested for hardness and disintegration time. The disintegration times of stored samples were measured using the MG method and compared with those of the initial samples.

**Effect of type of disintegration medium**

The five marketed commercial tablets were used in this study to compare the effect of using buffer instead of artificial saliva.

**Statistical Analysis**

The results of the experiments are given as a mean±S.D and were analyzed utilizing Student's t-test and one way analysis of variance (ANOVA) using Sigma Plot 11 software.

**Results and Discussion**

**Physical Properties of ODTs**

Table 3 shows that the friability of all prepared ODTs is within the accepted percent (less than 1%). The hardness of the 9 formulas was kept around 3.7 which is suitable in order to present the effect of type and concentration of superdisintegrant.

**Comparison of the disintegration time using the conventional disintegration test and the in vivotest**

The results of disintegration time for the prepared ODTs are shown in table 3; they are widely variable with high deviation by using conventional disintegration test, also indicates that the shortest disintegration time is reported for formula that contains 5% SSG. Meanwhile, the results of in vivo human sensory tests are reproducible with low standard deviation, and indicates that the 5% CP shows the shortest disintegration time within the single super-disintegrant, and in case of using 2 super-disintegrants, the combination of 5%CP with 10%MCC demonstrates the shortest disintegration time; these results are in agreement with those reported by many researchersthat workin the field of ODTs [19-21].

The results presented in figure 3 indicated that there was no correlation between the disintegration times determined by the conventional disintegration test and those of the human sensory test (R²=0.492), indicating that it was not accurate and reproducible to use the conventional disintegration test to determine the real oral disintegration time when the ODTs administrated by patient. Increasing the compression force during preparation of tablets significantly (p< 0.05) prolong the
disintegration time according to conventional disintegration method, while lower change was observed
in the disintegration time measured by human sensory test (Table 4) which reflect poor correlation
($R^2=0.779$) (Figure 4) between the conventional disintegration test and those of the human sensory test.
This effect may be attributed to the mechanical stress produced by the tongue in the mouth
[22]. Similar observations were noticed in disintegration time for the formula subjected to stress storage
conditions (Table 5 and Figure 4).

**Comparison of the disintegration time of the prepared ODTs using the new method (MG) and in vivo test**

The results of disintegration test of the prepared ODTs using the new method (MG) were reproducible
and closer to the human sensory test than in the conventional disintegration test, revealed by the high
 correlation coefficient (Table 3 and Figure 5) between the new method (MG) and the human sensory
test ($R^2=0.994$). Also high correlation was observed for formulas prepared under high force of
compression and stress storage condition (Figure 6).

**Disintegration time of commercial ODTs**

Five commercial ODTs of different weight, shape, and size were used for comparison between the
three methods of disintegration to confirm the results obtained with the prepared ODTs. The results
shown in Table 6 and Figure 7 indicated that there is no correlation between the disintegration time
of the conventional disintegration test and those of the human sensory test ($R^2=0.492$), while very high
correlation ($R^2=0.997$) was reported for the new method (MG) (Figure 8).

**Effect of disintegration medium on the disintegration time**

Saliva is very important in the ODTs, thus to investigate the significance of artificial saliva solution,
the phosphate buffer (pH 6.8) was used as disintegration medium. Although the results shown in Table 6
and Figure 8 indicated no significant ($p>0.05$) difference between artificial saliva solution and
the phosphate buffer (pH 6.8), but still the use of artificial saliva solution in the new method of
disintegration produce results with high correlation than when buffer is used. These results suggested
that the MG method, using artificial saliva solution, can be used to determine the disintegration time
and found comparable to the real disintegration in oral cavity. Although there are few trials performed
to develop disintegration tests, they are complicated and require special instruments [23].

The novel method presented in this study is highly similar to the real conditions of the oral cavity,
and take in consideration the two main factors that control the process of oral disintegration, the continuous
secretion of very small volume of saliva (about 1 ml/min) and removal from the mouth by
swallowing; the second is the mild mechanical force produced by the tongue on the upper jaw, which is
simulated in new method by the sponge of specific height that pushes the tablet up to the upper jaw. In
conclusion, the designed novel apparatus for determination of DT for ODTs is simple and
reproducible; it simulates the *in vivo* conditions to high degree with high correlation results compared
with disintegration in the human mouth.

**References**

Table 1. Formulation of blank orodispersible tablets

<table>
<thead>
<tr>
<th>Composition (mg)</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>
</tr>
</thead>
<tbody>
<tr>
<td>CCS</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SSG</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>20</td>
<td>10</td>
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<td>MCC</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Mg Stearate</td>
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<td>2</td>
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<td>2</td>
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<tr>
<td>Carb-O-Sil</td>
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<td>Mannitol</td>
<td>189</td>
<td>184</td>
<td>174</td>
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<td>174</td>
<td>184</td>
<td>174</td>
<td>164</td>
<td>154</td>
</tr>
<tr>
<td>Total weight</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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</tbody>
</table>

Table 2: Composition of artificial saliva solution (ASS)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disodium hydrogen orthophosphate (Na₂HPO₄)</td>
<td>0.426 g</td>
</tr>
<tr>
<td>Sodium bicarbonate (NaHCO₃)</td>
<td>1.680 g</td>
</tr>
<tr>
<td>Calcium chloride (CaCl₂)</td>
<td>0.147 g</td>
</tr>
<tr>
<td>Hydrochloric acid (HCL) 1N</td>
<td>Q.S to adjust pH to 6.8</td>
</tr>
<tr>
<td>Water (H₂O)</td>
<td>Up to 1.0 L</td>
</tr>
</tbody>
</table>

Figure 1. New disintegration apparatus (MG apparatus) for ODTs
Figure 2. Artificial oral cavity part of MG apparatus
Table 3. Evaluation physical parameters of prepared ODTs

<table>
<thead>
<tr>
<th>Formulas No.</th>
<th>Thickness (mm)</th>
<th>Hardness kg/cm²</th>
<th>Friability %</th>
<th>Conventional (\text{in vitro}) disintegration time (sec)</th>
<th>Human sensory disintegration time (sec)</th>
<th>New method (MG) disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.45±0.02</td>
<td>3.76±0.14</td>
<td>0.57</td>
<td>42.2±10.6</td>
<td>92.1±0.3</td>
<td>90.3±0.71</td>
</tr>
<tr>
<td>F2</td>
<td>3.44±0.01</td>
<td>3.76±0.16</td>
<td>0.65</td>
<td>17.6±4.4</td>
<td>57.2±0.74</td>
<td>59.3±0.83</td>
</tr>
<tr>
<td>F3</td>
<td>3.52±0.02</td>
<td>3.66±0.18</td>
<td>0.54</td>
<td>16.1±5.7</td>
<td>64.2±0.36</td>
<td>63.3±0.22</td>
</tr>
<tr>
<td>F4</td>
<td>3.48±0.01</td>
<td>3.69±0.16</td>
<td>0.58</td>
<td>15.3±4.8</td>
<td>53.1±0.52</td>
<td>52.2±0.33</td>
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<tr>
<td>F5</td>
<td>3.40±0.02</td>
<td>3.73±0.15</td>
<td>0.62</td>
<td>19.6±5.6</td>
<td>58.1±0.4</td>
<td>59.2±0.27</td>
</tr>
<tr>
<td>F6</td>
<td>3.49±0.01</td>
<td>3.74±0.17</td>
<td>0.42</td>
<td>18.8±4.6</td>
<td>50.2±0.37</td>
<td>49.1±0.31</td>
</tr>
<tr>
<td>F7</td>
<td>3.55±0.01</td>
<td>3.69±0.19</td>
<td>0.53</td>
<td>16.3±3.7</td>
<td>55.1±0.41</td>
<td>54.5±0.29</td>
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<tr>
<td>F8</td>
<td>3.52±0.02</td>
<td>3.76±0.20</td>
<td>0.60</td>
<td>15.4±2.5</td>
<td>28.1±0.56</td>
<td>26.1±0.21</td>
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<tr>
<td>F9</td>
<td>3.47±0.01</td>
<td>3.72±0.19</td>
<td>0.45</td>
<td>23.6±4.8</td>
<td>37.2±0.26</td>
<td>35.2±0.16</td>
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</table>
Table 4. Effect of compression force on physical properties of prepared ODTs

<table>
<thead>
<tr>
<th>Compression Force (KN)</th>
<th>Evaluated parameters</th>
<th>Conventional (in vitro) disintegration time (sec)</th>
<th>Human sensory disintegration time (sec)</th>
<th>New method (MG) disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hardness (\text{kg/cm}^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>6.4±0.76</td>
<td>26.8±1.4</td>
<td>44.1±0.75</td>
<td>45.3±0.91</td>
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<tr>
<td>30</td>
<td>8.3±1.1</td>
<td>28.7±1.3</td>
<td>51.4±1.33</td>
<td>50.6±1.6</td>
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<tr>
<td>35</td>
<td>11.1±1.76</td>
<td>80.4±2.4</td>
<td>59.3±1.43</td>
<td>61.6±1.41</td>
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</table>

Table 5. Effect of stress storage condition on physical properties of prepared ODTs

<table>
<thead>
<tr>
<th>Storage time (days)</th>
<th>Evaluation parameters</th>
<th>Conventional (in vitro) disintegration time (sec)</th>
<th>Human sensory disintegration time (sec)</th>
<th>New method (MG) disintegration time (sec)</th>
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<tbody>
<tr>
<td>0</td>
<td>Hardness (\text{kg/cm}^2)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>3.76±0.2</td>
<td>13.43±0.47</td>
<td>28.21±1.5</td>
<td>26.36±2.1</td>
</tr>
<tr>
<td>15</td>
<td>3.94±0.18</td>
<td>75.8±1.8</td>
<td>63.22±1.9</td>
<td>61.15±2.3</td>
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</table>

Figure 3. Relationship between DT \(in vivo\) and conventional \(in vitro\) DT of the prepared ODTs using different types and concentrations of superdisintegrants
Figure 4. Relationship between DT in vivo and conventional in vitro DT of the prepared ODTs at different forces of compression and stress conditions.

Table 6. Comparison of disintegration tests using commercial ODTs

<table>
<thead>
<tr>
<th>Commercial ODTs</th>
<th>Evaluated parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional in vitro disintegration time (sec)</td>
</tr>
<tr>
<td>Oronime (Nimesulide 100mg)</td>
<td>21.3±0.36</td>
</tr>
<tr>
<td>Olenaz Rapitab (Olanzapine 5mg)</td>
<td>25.4±0.87</td>
</tr>
<tr>
<td>Domstal -5 DT (Domperidone 5mg)</td>
<td>20.7±0.65</td>
</tr>
<tr>
<td>Nimulide-MD (Nimesulide 100mg)</td>
<td>30.9±0.53</td>
</tr>
<tr>
<td>Ketanov- MD (ketrolac 10mg)</td>
<td>28.7±0.98</td>
</tr>
</tbody>
</table>
Figure 5. Relationship between DT \textit{in vivo} and new method (MG) \textit{in vitro} DT on the prepared ODTs using different types and concentrations of super-disintegrants

Figure 6. Relationship between DT \textit{in vivo} and new method (MG) \textit{in vitro} DT on the prepared ODTs at different forces of compression and stress conditions
Figure 7. Relationship between DT \textit{in vivo} and conventional \textit{in vitro} DT on the commercially marketed ODTs

Figure 8. Relationship between DT \textit{in vivo} and new method (MG) \textit{in vitro} DT in commercially marketed ODTs using different disintegration media