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

Mowafaq Mohammed. Ghareeb,
Department of pharmaceutics, College of Pharmacy, Baghdad University, Baghdad, Iraq
Correspondence address: Tel: +9647901737638;
E-mail: mopharmacy@yahoo.com

Conflict of interest: none declared
Keywords: artificial oral cavity, orodispersible dosage form, disintegration test, MG apparatus
(Reveived:May 2012 , Accepted :June 2012)

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 orodipersible 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 2weeks). Also, five commercial orodispersible tablets were used to comparebetween 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, thenovelMG method is simple and highly correlated with the *in vivo* method and might be of value to predict disintegration time for orodispersible solid dosage forms.

تطوير تجويف فموي صناعي يستخدم لتقييم الوقت اللازم لتفتت الحبوب التي تتفت سريعا في الفم مختبريا

موفق محمد غريب
فرع الصيدلانيات,كلية الصيدلة,جامعة بغداد,بغداد, العراق
الهاتف:07901737638
البريد الالكتروني: mopharmacy@yahoo.com

مفتاح البحث: تجويف فموي صناعي، أشكال دوائية تتفتت في الفم، إختبار التفتت، جهازMG

الملخص

كثير من المرضى ومنهم كبار السن والاطفال لديهم صعوبة في بلع الادوية وخاصة الصلبة منها ,لذلك فان المستحضر الذي يتفتت سريعا في الفم هو حل لهذه المشكلة.

الحبوب التي تتفت في الفم هي تقنية مطورة حديثا وتعني انها تتفت اوتتحلل سريعا خلال عدة ثواني عندما توضع فوق اللسان بدون الحاجة للماء.

بالرغم من ان وقت التفتت يعتبر معيار رئيسي لتقييم اداء الحبوب السريعة التفتت, لكن لحد الان لاتوجد طرق دستورية بسيطة ودقيقة في المختبر وذلك لان حجم اللعاب قليل وكذلك سرعة تفتت الحبوب.

جهاز جديد وبسيط ر'كب بشكل يشبه التجويف الفموي وسمي جهاز(MG) يتكون بصورة رئيسية من موديل لفكي اسنان وخزان يغذي اللعاب ونظام تصوير فيديو.
لغرض تقييم الجهاز حضرت تسعة تركيبات لتكوين حبوب سريعة التفتت لاتحتوي على دواء باستخدام اربعة انواع من المفتتات المحسنة وبتراكيز مختلفة. اضافة الى تحضير واحدة من التركيبات باستخدام قيم مختلفة من قوة الضغط المسلط وكذلك تعرضها الى ظروف خزن مشددة(50درجة مئوية و75%رطوبة نسبية لمدة اسبوعين). كذلك استخدام خمسة انواع من الحبوب السريعة التفتت موجودة في الصيدليات لمقارنة تأثير استخدام المحلول المسيطر حامضيته بدل محلول اللعاب الصناعي. ستة عشر من المتطوعين شاركوا في تجربة الحبوب في افواههم.
أظهرت النتائج علاقة ربط عالية بين نتائج وقت التفتت باستخام الجهاز الجديد ونتائج المتبرعيين بينما لاتوجد علاقة ربط مع النتائج باستخدام الطريق التقليدية حسب دستور الادوية البريطاني. من الممكن الاستنتاج من نتائج البحث ان الطريقة البسيطة المقترحة ذات علاقة الربط العالية هي موعودة ومفيدة لتقييم وقت التفتت للحبوب السريعة التفتت.

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 orodispersibletablet as a tablet that can be placed in oral cavity where it disperses rapidly beforeswallowing [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 sensationwhich 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 providethe 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 waspurchased from (Teen Tech. Northants, U.K). Disodium hydrogen orthophosphate waspurchased 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

Pharmaceuticals Ltd., India);Nimulide-MD® tablets, (Panacea Biotec Ltd., India);and Ketanov MD® tablets, (Ranbaxy-India).

Preparation of blank ODTs

The ODTformulations 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 togetherin geometrical order for 10 min, and passed through sieve no. 18.The powdered mixture was then blended for 2 minwith 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/cm^2 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 wascalculated 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 ODTsaccording 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 readingswere reported[15].The artificial saliva solution was prepared according to the method proposed by Mariano*et al*(Table 2)[16].

Measurement of disintegration time byhuman sensory test

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

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

The Noveldisintegration 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 videoimages.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 1.0ml/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 disintegrationtimes 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 utilizingStudent'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 conventionaldisintegrationtest and the in vivotest

The results of disintegration time for the prepared ODTs are shown in table 3;they arewidely 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 ofODTs [19-21].

The results presented infigure 3 indicated that there was no correlation between the disintegrationtimes determined by the conventional disintegration test andthose of the human sensory test (R^2=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 administered by patient. Increasingthecompression forceduring 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 sensorytest than in the conventional disintegration test,revealed bythe high correlationcoefficient (Table 3 and Figure5) between the new method (MG) and thehuman 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 figure7 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 (pH6.8) 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 thatthe MG method,using artificial saliva solution,can be used to determine the disintegration timeand 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 1ml/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 is simulates the *in vivo* conditions to high degree with high correlation results compared with disintegration in the human mouth.

References

1. Hirani JJ, Rathod DA, Vadalia KR. Orally disintegrating tablets: a review. Trop J Pharm Res 2009; 8(2):161-172.
2. Seagr H. Drug delivery products and the zydis fast dissolving dosage forms. J Pharm Pharmacol 1998;50(4):375-382.
3. Hanawa T, Watanabe A, Tsuchiya T, Ikoma R, Hidaka M, Sugihara M. New oral dosage form for elderly patients: preparation and characterization of silk fibroin gel. Chem Pharm Bull 1995; 43(2):284-288.
4. Suresh S, Pandit V, Joshi HP. Preparation and evaluation of mouth dissolving tablets of salbutamol sulphate. Ind J Pharm Sci 2007; 69(3):467-469.
5. Rozer R, Riegelman S, Yang KY, Cheng KC. Fast dissolving drug delivery systems: techniques and methods. EurRespir J 1998; 12:315-320.

6. US Food and Drug Administration, CDER Data Standards Manual. 2003. http://www.fda.gov/ cder/dsm/DRG/drg00201.htm.Accessed 6 February 2007.
7. European Directorate for quality of Medicines. Pharmaeuropa 1998; 10(4):547.
8. Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity.Chem Pharm Bull1996;44(11):2121-2127.
9. Morita Y, Tsushima Y, Yasui M, Termoz R, Ajioka J, Takayama K. Evaluation of the disintegration time of rapidly disintegrating tablets via a novel method utilizing a CCD camera. Chem Pharm Bull 2002;50(9):1181-1186.
10. El-Arini SK, Clas SD. Evaluation of disintegration testing of different fast dissolving tablets using the texture analyzer. Pharm DevTechnol 2002;7(3):361-371.
11. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier JP, PiccerelleP. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int J Pharm 2005; 292(1-2):29-41.
12. Lagerlöf F, Dawes C. The volume of saliva in the mouth before and after swallowing. J Dent Res. 1984 May;63(5):618-21.
13. Chaudhari P, Chaudhari S, Kohle S, Dave K, More D. Formulation and evaluation of fast dissolving tablets of famotidine. Indian Drug 2005; 42:641-649.
14. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. Int J Pharmacy Pharm sci2009; 1(1):219-226.
15. Panigrahi D, Baghel S, Mishra B. Mouth dissolving tablets: An overview of preparation techniques, evaluation and patented technologies. J Pharm Res 2005; 4(3):33-38.
16. Mariano N, Oliveira R, FenandesM, RigoO E. Corrosion behavior of pure titanium in artificial saliva solution. RevistaMateria 2009; 14(2):878- 880.
17. Ogata K, Takamura N, Kashiwagi S, Hamada R, Kozima Y, Arimori K.Evaluation on disintegration tests of rapidly-disintegrating tablets.JpnJ Pharm Health Care Sci 2001; 27:553-558.
18. John R Williams. The declaration of Helsinki and public health. Bull World Health Organ. 2008 August; 86(8): 650–652.
19. Battu SK, Repka MA, Majumdar S, Madhusudan RY. Formulation and evaluation of rapidly disintegrating fenoverine tablets: effect of superdisintegrants. Drug DevInd Pharm2007;33(11):1225-1232.
20. Keny RV, Chrisma D, and Lourenco CF. Formulation and evaluation of rizatriptan benzoate mouth disintegrating tablets. Indian J Pharm Sci2010; 72(1):79-85.
21. Ahmed AE, Afaf AR, Ihab RB, Dalia AM. Formulation and evaluation of taste masked rapidly disintegrating tablet containing flupentixoldihyrochloride. IntResJ Pharm 2011; 2(9):58-64.
22. Dali S, Subhashis C, Sanjay S, Brahmeshwar M. Mouth dissolving tablets II: An overview of evaluation techniques.Sci Pharm 2009; 77:327-341.
23. Kakutani R, Muro H, Makino T. Development of a new disintegration method for orally disintegrating tablets. Chem Pharm Bull (Tokyo) 2010;58(7):885-890.

Table 1. Formulation of blank orodispersible tablets

Composition (mg)	Formula No.								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
CCS	5	10	20	-	-	-	-	-	-
SSG	-	-	-	10	20	-	-	-	-
CP	-	-	-	-	-	10	20	10	20
MCC	-	-	-	-	-	-	-	20	20
Mg Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Carb-O-Sil	2	2	2	2	2	2	2	2	2
Mannitol	189	184	174	184	174	184	174	164	154
Total weight	200	200	200	200	200	200	200	200	200

Table 2: Composition of artificial saliva solution (ASS)

Ingredients	Quantity
Disodium hydrogen orthophosphate (Na_2HPO_4)	0.426 g
Sodium bicarbonate ($NaHCO_3$)	1.680 g
Calcium chloride ($Cacl_2$)	0.147 g
Hydrochloric acid (HCL) 1N	Q.S to adjust pH to 6.8
Water (H_2O)	Up to 1.0 L

Figure 1. New disintegration apparatus (MG apparatus) for ODTs

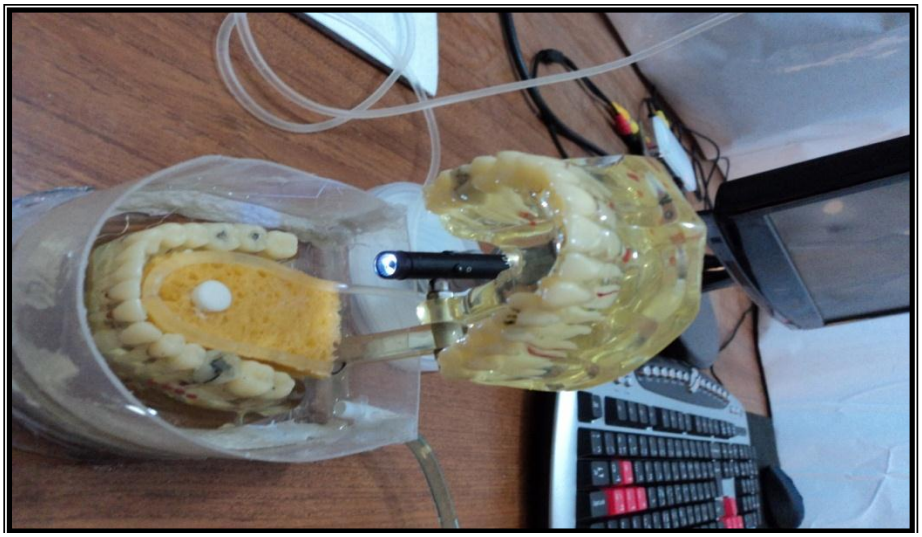

Figure 2. Artificial oral cavity part of MG apparatus

Table 3. Evaluation physical parameters of prepared ODTs

Formulas No.	Evaluated parameters					
	Thickness (mm)	Hardness kg/cm^2	Friability %	Conventional *in vitro* disintegration time (sec)	Human sensory disintegration time (sec)	New method (MG) disintegration time (sec)
F1	3.45±0.02	3.76±0.14	0.57	42.2±10.6	92.1±0.3	90.3±0.71
F2	3.44±0.01	3.76±0.16	0.65	17.6±4.4	57.2±0.74	59.3±0.83
F3	3.52±0.02	3.66±0.18	0.54	16.1±5.7	64.2±0.36	63.3±0.22
F4	3.48±0.01	3.69±0.16	0.58	15.3±4.8	53.1±0.52	52.2±0.33
F5	3.40±0.02	3.73±0.15	0.62	19.6±5.6	58.1±0.4	59.2±0.27
F6	3.49±0.01	3.74±0.17	0.42	18.8±4.6	50.2±0.37	49.1±0.31
F7	3.55±0.01	3.69±0.19	0.53	16.3±3.7	55.1±0.41	54.5±0.29
F8	3.52±0.02	3.76±0.20	0.60	15.4±2.5	28.1±0.56	26.1±0.21
F9	3.47±0.01	3.72±0.19	0.45	23.6±4.8	37.2±0.26	35.2±0.16

Table 4. Effect of compression force on physical properties of prepared ODTs

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

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

Storage time (days)	Evaluation parameters			
	Hardness kg/cm^2	Conventional *in vitro* disintegration time (sec)	Human sensory disintegration time (sec)	New method (MG) disintegration time (sec)
0	3.76±0.2	13.43±0.47	28.21±1.5	26.36±2.1
15	3.94±0.18	75.8±1.8	63.22±1.9	61.15±2.3

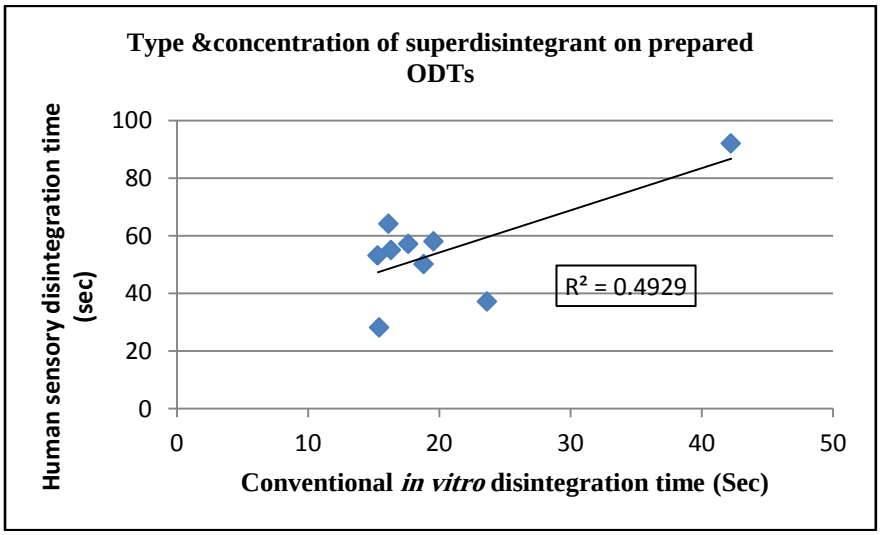

Figure 3. Relationship between DT *in vivo* and conventional *in vitro* DT of the prepared ODTs using different types and concentrations of super-disintegrants

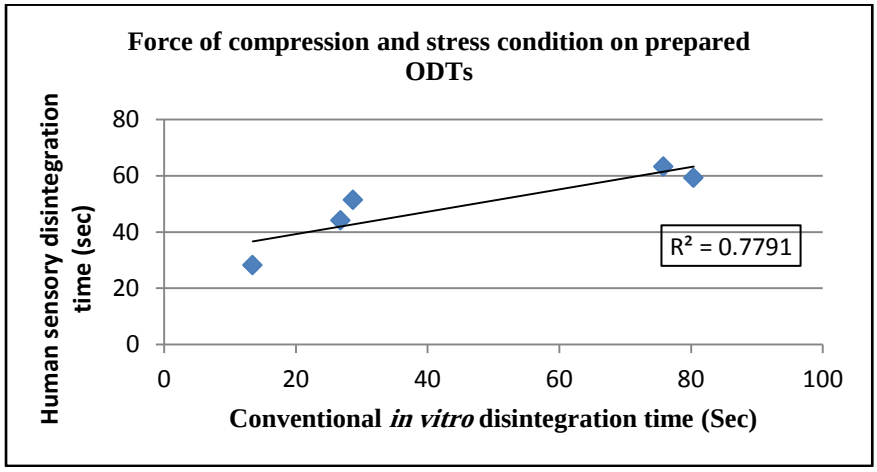

Figure 4. Relationship between DT *in vivo* and conventional *in vitro* DT of the prepared ODTs at different forces of compression and stress conditions

Table 6. Comparison of disintegration tests using commercial ODTs

Commercial ODTs	Evaluated parameters			
	Conventional *in vitro* disintegration time (sec)	Human sensory disintegration time (sec)	New method (MG) disintegration time (sec) Artificial saliva solution	New method (MG) disintegration time (sec) Phosphate buffer
Oronime(Nimesulide 100mg)	21.3±0.36	34.6±2.5	31.2±0.54	33.4±0.74
OlenazRapitab (Olanzepine 5mg)	25.4±0.87	42.7±0.97	40.4±0.94	44.7±0.77
Domstal -5 DT (Domperidone 5mg)	20.7±0.65	64.6±1.12	59.56±1.42	63.7±1.80
Nimulide-MD (Nimesulide 100mg)	30.9±0.53	84.6±3.4	79.5±1.60	82.2±1.20
Ketanov- MD (ketrolac 10mg)	28.7±0.98	67.2±2.3	64.6±1.20	68.3±1.90

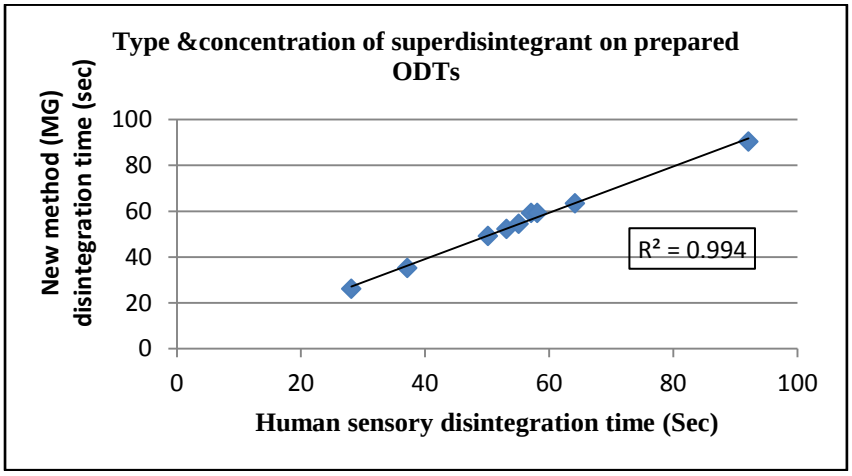

Figure 5. Relationship between DT *in vivo* and new method (MG) *in vitro* DT on the prepared ODTs using different types and concentrations of super-disintegrants

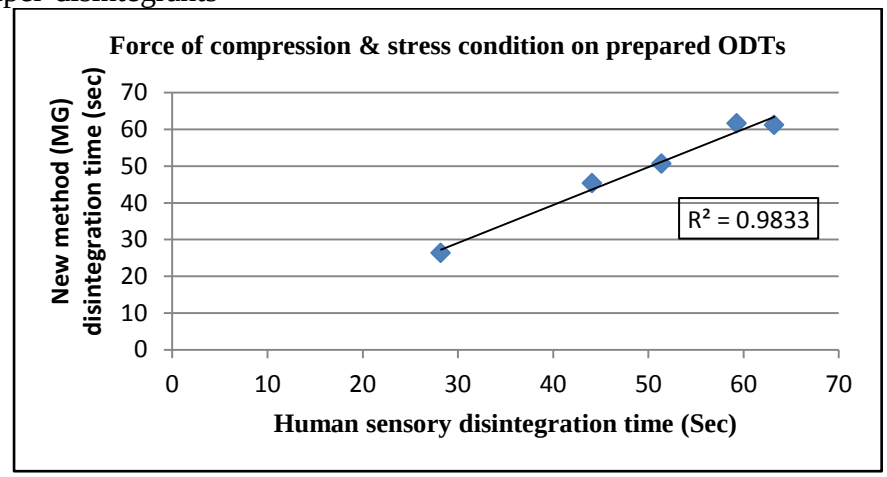

Figure 6. Relationship between DT *in vivo* and new method (MG) *in vitro* DT on the prepared ODTs at different forces of compression and stress conditions

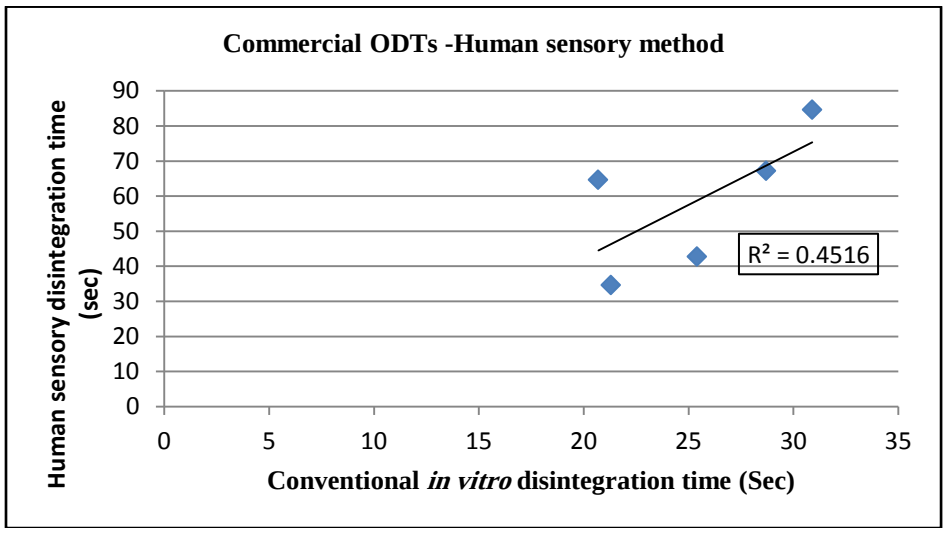

Figure 7. Relationship between DT *in vivo* and conventional *in vitro* DT on the commercially marketed ODTs

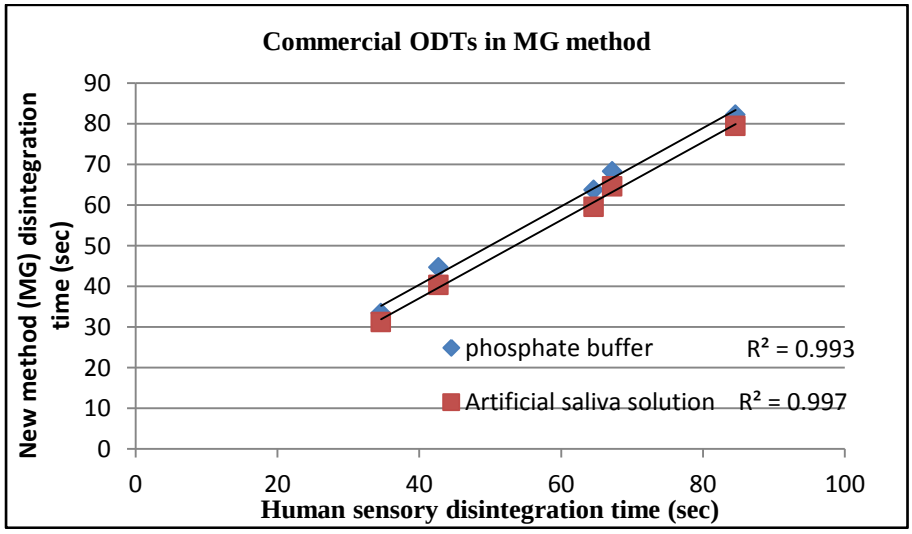

Figure 8. Relationship between DT *in vivo* and new method (MG) *in vitro* DT in commercially marketed ODTs using different disintegration media