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A new modified wetting test and an alternative disintegration test for orally disintegrating tablets

Patrick Hooper, Jason Lasher, Kenneth S. Alexander, Gabriella Baki*

University of Toledo, College of Pharmacy and Pharmaceutical Sciences, Department of Pharmacy Practice, 3000 Arlington Ave., Toledo, OH 43614, USA

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ABSTRACT

Industrial manufacturing of solid oral dosage forms require quality tests, such as friability, hardness, and disintegration. The United States Pharmacopeia (USP) disintegration test uses 900 mL of water. However, recent studies of orally disintegrating tablets (ODTs) have shown that this volume does not accurately portray the oral environment. In our study, various tests were conducted with a more moderate amount of water that accurately resembles the oral environment. A simulated wetting test was performed to calculate the water absorption ratio. Results showed that wetting was comparable to disintegration. Although the wetting test worked for most types of ODTs, it had limitations that produced inaccurate results. This led to the use of a modified shaking water bath test. This test was found to work for all types of ODT products and was not subject to the limitations of the wetting test. The shake test could provide disintegration times rather than water permeation times; however, it could not be used to calculate the water absorption ratio. A strong correlation was observed between the standardized shake test and the USP disintegration times for the tablets. This shake test could be used during the development stages and quality tests for ODTs with relative ease.

1. Introduction

Orally disintegrating tablets (ODTs), also known as fast dispersing, fast melting, rapid melt, and orodispersible systems, are gaining importance and popularity among novel oral drug delivery systems as they are convenient to administer and they can offer improved patient adherence. The US Food and Drug Administration (FDA) Center for Drug Evaluation and Research states in their 2008 guidance that an ODT is "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue [1]." As ODTs are designed to quickly disintegrate in the saliva, they do not require chewing or the aid of water, which is highly beneficial in the pediatric and geriatric populations as well as in patients with conditions related to impaired swallowing [2,3].

The main factor in categorizing a product as an ODT is its disintegration time. The FDA guidance outlines that an ODT should disintegrate rapidly with an *in vitro* disintegration time of approximately 30 s or less according to the United States Pharmacopeia (USP) disintegration method or alternative. Although an explicit tablet diameter and weight is not stated within the guidance, it is recommended that the tablet does not exceed 500 mg considering patient safety and compliance.

In spite of the importance of disintegration time from a regulatory perspective, currently there is no standard test in the USP specifically designed for ODTs. USP <701>, the general disintegration test used for regular tablets, requires products to be tested in 900 mL of water with rapid and vigorous agitation. Although this amount of water aids in the disintegration of the tablets, it does not accurately portray the conditions of the oral cavity, and does not provide a strong correlation to an *in vivo* disintegration time. It has been shown that the average rate of saliva secretion is approximately 0.2–0.4 mL/min when resting, and it could be increased up to 2 mL upon stimulation [4].

The FDA guideline also states that alternative tests can be employed to obtain disintegration time for ODTs if the method can be correlated with or are demonstrated to provide results equivalent to the USP method [1]. In order to attain a more accurate *in vitro-in vivo* correlation (IVIVC), a variety of alternative disintegration methods have been proposed. Some of these methods involve placing a folded tissue or a circular filter paper in a petri dish followed by the addition of water containing a water soluble dye. The tablet is then placed on the wetted paper and the time needed for disintegration into particles is noted as the

* Corresponding author.
E-mail address: Gabriella.Baki@utoledo.edu (G. Baki).

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disintegrating time [5]. A modified version of this test uses a Whatman filter paper disk in a Corning 12-well polystyrene microplate to which a set amount of dye solution is added. The tablet is then placed on the paper. The volume of the aqueous solution is based on tablet weight. The wetting time, defined by the authors as the time required for the aqueous solution to diffuse through the tablet and completely cover the surface of the tablet, is measured and recorded as the simulated disintegration time. This method is referred to as the simulated wetting test [6]. An additional method involves a texture analyzer that accurately determines the disintegration time [7]. This machine has a cylindrical probe that penetrates a tablet, which is immersed in a liquid medium. The distance traveled by the probe is generated into a plot by software, which provides a profile for the tablet. Although this is an accurate test method, such equipment can be quite expensive. Additional simple methods have been proposed, including water baths, rotary shafts, and modified USP tests [8–14]. However, there is no standardized alternative testing method that could help acquire realistic disintegration time of an ODT, and many of the proposed tests do not provide adequate IVIVC.

In many studies wetting time is correlated with the disintegration time of an ODT. The wetting test method however varies from study to study. The purpose of this current study was to create and standardize a simulated wetting test (SWT) that accurately portrays the oral environment. The newly proposed method could give an accurate and reproducible wetting time for a given tablet with a moderate amount of ease. The main goals of this study were to simulate the oral environment, including the amount of saliva typically present in the mouth and on the surface of the tongue and its even distribution in the oral cavity. While this new test method could give a reproducible wetting time, it could also provide a water absorption ratio (AR) for the tablet. AR refers to the amount of water permeated into the tablet after it has been wetted completely. This parameter could be used during the formulation and evaluation of ODTs.

In this study a proposed alternative disintegration test is performed and is compared to a new SWT. The alternative disintegration time mimics the SWT in regards of more accurately simulating the oral environment compared to the USP disintegration method. Both methods can be used as a quick screening tool during formulation to evaluate and discern if a product could be labeled as an ODT.

2. Materials and methods

2.1. Materials

Trehalose (Lot No. 2F101) used as the filler and sweetener was obtained from The Endowment for Medical Research and Cargill (Wayzata, MN). Primojel® (Lot No. 44020-7356) provided by DFE Pharma (Goch, Germany) was used as the superdisintegrant. Microcrystalline cellulose (Avicel PH 200, Lot No. M710C) provided by FMC Corporation was used as the binder. Talc powder (Lot No. 10151214) was used as a lubricant and glidant and was purchased from Letco Medical Supplies (Decatur, AL). Magnesium stearate (Lot No. 742748) used as a lubricant was purchased from Fisher Scientific (Fair Lawn, NJ). Deionized (DI) water was supplied by the University of Toledo Health Science Campus (Toledo, OH) deionization system. FD&C Blue 1 (Lot #SL1127) obtained from Spectrum Chemical MFG Corp., was used as a dye to make tablet wetting more visible.

Commercial products included Claritin Reditabs® (distributed by MSD Consumer Care Inc.), Children's Zyrtec® cetirizine HCl 10 mg (distributed by McNeil consumer Healthcare), Unisom® Quickmelts™ diphenhydramine HCl 25 mg (distributed by Chattem Inc.), Alavert® (distributed by Pfizer Inc.), Major® Loratidine 10 mg (distributed by Major Pharmaceuticals), St. Joseph® low dose aspirin (distributed by St. Joseph Health Products LLC), and Zicam Rapidmelts® (distributed by Matrixx Initiatives, Inc.), which were all purchased at a local Walmart store (Toledo, Ohio).

2.2. Methods

2.2.1. Preparation of powder mixtures for blank ODTs

The powders for the 100 mg, 300 mg and 500 mg blank ODTs were mixed using ingredients in the following ratio: 73.5% trehalose, 20.0% microcrystalline cellulose, 4.0% Primojel, 2.0% talc, and 0.5% magnesium stearate. All ingredients except for magnesium stearate were blended for 8 min, then magnesium stearate was added to the mixture and it was blended for 2 additional minutes using a Turbula mixer (Clifton, NJ). The speed of rotation was 50 rpm.

Table 1
Types of materials with dimensions and the volumes of 0.1% Blue 1 solution used for the modified simulated wetting tests along with the average tablet wetting time using 300 mg blank ODTs ($n = 6$, ±SD).

Code	Type of material	Dimension	Volume of 0.1% Blue 1 solution (mL)	Wetting time (seconds)
M1	Paper towel	10 cm × 10 cm folded in half twice	5	13.20 ± 1.84
M2	Whatman circular filter	7.0 cm diameter (layered 5 times)	10	21.42 ± 2.59
M3	Facial buff sponge (Studio M®) of circular shape	6.5 cm diameter, 1.0 cm thickness	10	43.16 ± 9.43
M4	Ulta® premium cotton pads of circular shape	7.5 cm diameter, 0.5 cm thickness	10	17.85 ± 1.24
M5	Dual textured circular cotton rounds (Swisspers®)	5.5 cm diameter, 0.3 cm thickness (both sides tested)	10	(Quilted) 14.92 ± 2.1 (flat) 14.87 ± 0.52
M6	Make-up micro sponge (latex free)	5.5 cm diameter, 0.8 cm thickness	10	35.72 ± 2.98
M7	O-CEL-O™ sponge	2.3 cm thickness	5	19.62 ± 1.4
M8	Dawn® premium cellulose sponge cloth	0.5 cm thickness	2	19.14 ± 0.39
M9	Sephora facial cellulose sponge	1.0 cm thickness	2	18.85 ± 0.64
C1	No absorbing material in a petri dish	N/A	10	8.21 ± 1.12
C2	No absorbing material in a 20 mL beaker	N/A	1.5 1.75 2	11.50 ± 1.2 9.90 ± 0.41 8.75 ± 0.40