A New Test Unit for Disintegration End-Point Determination of Orodispersible Films

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ABSTRACT: No standard time or pharmacopoeia disintegration test method for orodispersible films (ODFs) exists. The USP disintegration test for tablets and capsules poses significant challenges for end-point determination when used for ODFs. We tested a newly developed disintegration test unit (DTU) against the USP disintegration test. The DTU is an accessory to the USP disintegration apparatus. It holds the ODF in a horizontal position, allowing top-view of the ODF during testing. A Gauge R&R study was conducted to assign relative contributions of the total variability from the operator, sample or the experimental set-up. Precision was compared using commercial ODF products in different media. Agreement between the two measurement methods was analysed. The DTU showed improved repeatability and reproducibility compared to the USP disintegration system with tighter standard deviations regardless of operator or medium. There is good agreement between the two methods, with the USP disintegration test giving generally longer disintegration times possibly due to difficulty in end-point determination. The DTU provided clear end-point determination and is suitable for quality control of ODFs during product developmental stage or manufacturing. This may facilitate the development of a standardized methodology for disintegration time determination of ODFs. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:3893–3903, 2015
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INTRODUCTION

The orodispersible film (ODF) is designed to disintegrate quickly in the buccal cavity for rapid drug absorption, circumventing the need for swallowing. This eliminates problems of choking and lack of access to drinking water. ODFs are suitable for patients with issues related to administration of oral medications such as dysphagia and poor compliance. These patient populations include paediatrics, geriatrics the mentally challenged and oncology patients who may experience post-treatment nausea.[1,2] ODFs deliver a fixed drug load, thus offering improved dosing accuracy over oral solutions and suspensions given by mouth without the need to use measuring-dosing devices.[3] These benefits have led to the growing popularity of ODFs as an alternative oral dosage form to tablets, capsules and liquid medications.

The European Pharmacopoeia (E.P.) 8.0 recently included the ODF in the "oromucosal preparations" monograph, indicating its benefits as a drug delivery system.[4] The EP 8.0 definition states that ODFs should "disintegrate rapidly." However, this is not accompanied with a specified time limit. Considering that ODF disintegration behaviour is crucial to quality and safety, it is imperative that ODFs disintegrate fully within a set time frame to prevent choking or aspiration and to provide good mouth feel.[5–7] These factors affect patient compliance. The disintegration also needs to be rapid for quick drug delivery with rapid onset as dictated by the treatment indications. Therefore, specification of the time for disintegration of ODF products is essential before their commercialisation.

A suitable disintegration test for ODFs is a necessary inclusion to pharmacopoeias to quantify the disintegration time in order to guide development of ODFs and verify the quality of the product. Several disintegration test methods for ODFs are undergoing development and have been described in the literature (Table 1). These tests quantify or predict disintegration times either with the use of small media volume on mobile or immobilised ODFs; modified pharmacopeial disintegration tests using large media volume; or the measurement of swelling behaviour of ODFs upon hydration. Small media volume tests aim to be biorelevant and are applied to mimic the oral cavity volume or saliva volume. Swelling studies to predict disintegration time has been applied by some groups. Modified pharmacopeial disintegration tests apply the use of conventional disintegration testers.

The above methods faced challenges with the end-point determination of the disintegration of the ODF, leading to inconsistencies in results. In some cases, the end-point may not be well defined, yielding wide ranging results among users. The use of disks, weights or paper clips may underestimate the disintegration time because of additional forces exerted on the ODF during the test. Researchers have also applied the standard disintegration test, without modifications, to ODFs.[8–11] The pharmacopoeia disintegration test for tablets and capsules cannot be directly adapted to ODFs because of challenges in end-point determination. Consequently, these previous test methods may be unsuitable in giving consistent results for quality control.

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Table 1. Summary of Modified Disintegration Test Methods in Literature

	Name	Volume of Media	Film Mobility	Description	Ref.
Small volume	Petri dish method 1	25 mL	Mobile	The ODF is added to water. A gentle swirling motion is applied every 10 s until disintegration is observed.	8
	Petri dish method 2	2 mL	Mobile	The water is added to the ODF. A gentle swirling motion is applied every 10 s until disintegration is observed.	9
	Slide frame method	One drop	Immobile	The ODF was clamped into slide frames and placed horizontally over a petri dish. A drop of water was pipetted onto the ODF and the time until the water bored a hole was taken as the disintegration time.	10
	Diffusion apparatus	n/a	Immobile	Wafers placed on a stainless steel wire mesh in donor compartment of diffusion apparatus. It is wetted on the underside by contact with distilled water in the receiver compartment. Hydration is observed in one direction via high-speed camera. Time to complete hydration and total disintegration were taken as disintegration time.	11
	Wire mesh method	10 mL	Immobile	A stainless steel wire mesh is used to support the ODF, whereas water was added and disintegration of the ODF through the wire mesh was observed visually or via high-speed camera.	12
Swelling	Contact angle measurement	7.5 μL	Immobile	Contact angle measurement between a drop of water and the planar surface of the ODF with the developed drop shape analysis apparatus.	10
	Thermomechanical analysis	250 μL	Immobile	The swelling of the ODF upon addition of a small amount of water was measured.	13
	Swelling behaviour	15 mL	Mobile	The degree of swelling by calculating the weight change of the ODF before and after water submersion.	14
Large volume	USP disintegration tester	700 mL	Immobile	ODFs held in paper clips and dropped into the USP disintegration tester with no modification to test speed and stroke.	15
	Modified disintegration apparatus 1	500–700 mL	Immobile	Use of a sample holder to hold the ODFs vertically in the disintegration tester with weights attached to allow viewing of disintegration end-point.	16
	Modified disintegration apparatus 2	500–700 mL		ODFs held vertically by clamps onto the arm of a disintegration tester that moved the ODF in and out of a water bath at a modified speed and stroke.	17

An appropriate disintegration test for ODFs with clear end-point is needed. In this report, we present the development and evaluation of a new disintegration test unit (DTU) that can be incorporated as an accessory to the USP disintegration system. The modified disintegration test using the DTU was compared with the USP disintegration test using commercially available ODFs.[12] The ease and precision for end-point determination and the consistency of measured disintegration times among operators were assessed. The effects of different disintegration media on the disintegration time of ODFs for both experimental setups were also investigated.

Materials and Methods

Materials

All ODF products were obtained commercially: Donepezil-HCl HEXAL® (DON; HEXAL AG, Holzkirchen, Germany), Gas-X Extra Strength (GX; Novartis, New Jersey, United States), Risperidone HEXAL® (RIS; HEXAL AG, Holzkirchen, Germany), ZenTrip (ZEN; Sato Pharmaceutical Company Ltd., Tokyo, Japan), Listerine breath strips (LIS; Johnson & Johnson Healthcare, New Jersey, United States), melatonin natural mint chocolate strips (MEL; Jamieson Laboratories, Ontario,

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