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An overview of disintegration testing for oral disintegrating tablets (ODTs)

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Abstract

Orally disintegrating tablet (ODT) prescriptions are often written. ODTs are among the most preferred dose forms for a number of demographics, including kids and the elderly. These are solid dose forms that, as soon as they come into touch with saliva in the patient's mouth, are meant to dissolve or disintegrate extremely fast. The United States Pharmacopeia (USP) states that in order to guarantee consistency and efficacy, each dosage form must successfully complete a series of quality control tests. The disintegration test is essential for ODTs in order to determine how long it takes for tablets to decompose and release their contents for absorption and dissolution. It is also an essential predictive test for figuring out the relationship between in vitro and in vivo. As mentioned in the USP, however, there are no required uniform disintegration testing requirements for ODTs. Recent USP, on the other hand, relates to particular manufacturer monograph standards, which might differ between monographs. This article elaborates on the benefits and drawbacks of a number of developed disintegration tests and methods for ODTs, including basket rack assembly, CCD camera, texture analyzer (TA), special disintegration equipment, prototype disintegration tester (PDT), simple approach, and modified wetting test.

Keywords: USP physical test, disintegration test, oral disintegrating tablets (ODTs), super disintegrants

INTRODUCTION

Orally disintegrating tablet (ODT) is an emerging and important dosage form in pharmaceutical market. It was developed by R.P. Scherer Corporation in 1986 and was first introduced into Swedish market as Zydis technology to formulate famotidine ODT in 1993[1]. Approval by FDA was done in 1996 for its use to formulate Claritin RediTabs by Schering-Plough. Currently, numerous other ODT technologies by several pharmaceutical companies and research groups are available as well [2]. Orally disintegrating tablet ODT formulations were mainly developed for existing drugs. This is because it extends product self-life, expands solid dosage form market, and avoids counterfeiting. Oral disintegrating offers ease of administration, and convenience for special populations like patients who cannot swallow tablets (pediatrics and geriatrics), patients with swallowing difficulties (dysphagia), or those who have limited access to water. Some ODT formulations allow for a high drug load, leave no grittiness or sandy feeling in mouth, allow for masking taste of bitter drugs via drug encapsulation, coating, or by using various excipients, and provide good stability. In addition to convenience of administration, ODT formulations allowed for extending product life-cycle for manufacturers, expanded market size for solid dosage forms, and reduced counterfeiting potential. Formulation of ODT has been studied as a way of improving bioavailability of poorly water-soluble drugs and it has been observed that ODT increases the bioavailability of such drugs [3]. There are various challenges involved in formulation and development of ODT which include achieving adequate tablet hardness, accommodating high drug load, efficiently masking a bitter taste, leaving a good mouth feel following tablet disintegration, avoiding additional costs for special packaging required for friable tablets, and maintaining physical and chemical drug stability during storage [3].

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Disintegration mechanisms of ODTs

Other names for ODT include orodisperse, quick-dissolving system, mouth dissolving tablets, fast melting tablets, fast disintegrating tablet (FDT), fast dissolving tablet (FDT), fast dissolving tablet (RDT), rapid dissolving tablet (RDT), and orally dissolving tablet (ODT). United States Food and Drug Administration (US FDA) defined orally disintegrating tablets (ODTs) as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [4]. In special patient populations like geriatrics and pediatrics, its ease of use is crucial for improving patient compliance, making it dosage form of choice [5]. Orally disintegrating tablets are made with specialized functional recipients that are meant to dissolve quickly in the mouth without need for chewing, crushing, or presence of a lot of liquid [2].

There are two main forms of ODTs namely; freeze-drying manufacturing tablets (lyophilization) and loosely compressed tablets. The freeze-drying procedure is used to increase dissolution rate and oral bioavailability of medicines that have low solubility but high permeability (biopharmaceutical classification system Class II drugs). Freeze drying (Lyophilization) involves removal of water from a product after it has been frozen. This process is carried out in a variety of ways to produce the same end product. In this method, the drug is physically trapped in a water-soluble matrix (a water-soluble mixture of saccharide and polymer formulated to provide rapid dispersion and physical strength), which is then freeze-dried to produce a product that dissolves quickly when placed in the mouth. One of the most successful freeze-drying technologies is called Zydis process. Zydis technology uses a proprietary freeze-drying technique to create completed dose units that differ greatly from standard oral systems. With this technology, a medication solution or suspension in water is poured into pre-fabricated blisters (giving tablet shape) and then frozen in a specifically engineered cryogenic freezing process to manage size of ice crystals, ensuring that the tablet has a porous matrix for quick disintegration. Frozen units are then transferred to large-scale freeze dryers for sublimation process, in which moisture from the tablets is evaporated and open blisters are sealed using heat seal method [6]. Once a tablet comes in contact with a liquid medium, the super disintegrants swell, deform, or wick up the liquid, thus increasing tablet volume. This results in break-up and disintegration. Extent of water uptake as well as rate at which water uptake develops are very important for tablets to disintegrate. Conventional equipment and limited number of steps in his method, make it most cost-effective method for manufacturing ODT. According to guidelines developed by FDA, regulation, and accreditation of ODT is an ongoing process that needs continuous review to ensure quality and efficiency for human use. Accreditation process for new drugs is usually an annual exercise though review of quality is continuous [6].

FDA ODT guidelines vs. USP disintegration test

Disintegration tests are a commonly used USP method to investigate disintegration time *in vivo* and to assist during solid dosage form development [6]. Disintegration time is defined as time it takes for an oral dosage form to disintegrate into small particles under designed experimental conditions [7]. United States Pharmacopoeia (USP) tests are intended to provide specific quality control tests to ensure standard product performance for finished products. Therefore, current USP disintegration test using basket-rack assembly provides only pass/fail results following a specific time. In this test, a large volume of disintegration medium is utilized to evaluate tablet disintegration as well as forceful continuous vertical motion of tested tablets. This test was initially designed to test the disintegration of conventional tablets that disintegrate and release their active ingredient in the presence of large acidic aqueous volume and vigorous motility of the stomach over an extended period.

Orally disintegrating tablets (ODTs) have a disintegration time of approximately 30 s or less and recommended tablet weight should be less than 500 mg. However, USP disintegration test using basket-rack assembly does not resemble a static environment and small salivary volumes with almost a neutral pH in oral cavity. Also, due to fast disintegration of ODT formulations (< 30 s), actual disintegration end-point is easily missed by time required for ODTs to be placed in apparatus, basket to be lowered, time for apparatus to be started and stopped, and basket to be raised again for visual inspection, which definitely cannot be accounted for within 30 s specified by FDA. Furthermore, this basket-rack assembly test cannot be utilized for product development and comparison of various ODT formulations using various functional excipients and manufacturing methods [9]. Therefore, according to 2016 edition of USP, disintegration testing for ODTs is referred to as the testing method and standards utilized by the manufacturer as prescribed in individual monographs of ODT products. These guidelines have created several testing methods and standards rather than one universal method and standards for all ODTs.

Disintegration tests for ODTs

To accurately measure the disintegration time of ODTs in conditions that resemble *in vivo*

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environments, various techniques have been developed. Development of these tests was crucial for product development and optimization that facilitated studying various factors that affect rapid tablet disintegration including type and grade of excipients used, manufacturing methods, and settings. Also, it encouraged studies investigating effect of various ODT formulations containing various excipients and drug loads on pharmacokinetics and bioavailability of active ingredients. Based on factors that researchers believed to have a great impact on ODT's ability to disintegrate, different disintegration equipment designs and testing procedures were developed.

Basket-rack assembly (USP)

Basket-rack assembly is USP method used to describe ODT disintegration process and apparatus in addition to measuring an estimation of the time it takes for an ODT to disintegrate [9,10]. Through this process, open-ended tubes are vertically held by plates and woven by stainless steel wires. Tablets are placed in tubes and lowered into beakers after which baskets are raised and lowered into 900 mL immersion medium at constant frequencies until full disintegration. The process is repeated on tablets that take long to disintegrate to help calculate the average time it takes for such tablets to fully disintegrate. This method is good as it allows for physical observation of disintegration process in addition to allowing multiple experimental performances to help determine actual disintegration time [9].

Basket-rack apparatus is prepared in a uniformly standard measure to help provide consistent results. This apparatus may be varied in design but specifications of glass tubes and screen meshes need to be constantly maintained [9]. Disintegration process is monitored through a glass apparatus and the end-time of operation is recorded. This method has the challenge of being a confusing process, has no good correlation with *in vivo* tablet disintegration, and volume of medium used is not applicable in oral cavity.

Novel method utilizing a CCD camera

This new method involves use of CCD cameras to help evaluate disintegration of ODTs. It was designed to help complement the Japanese Pharmacopoeia (JP) XIII disintegration test that measures the dissolution of orally disintegrating tablets among elderly people in society [11]. This study is predicated on observation that methods for detecting disintegration rate of ODTs, such as JP XII, are ineffective due to agitation impact they produce. As a result, this method complementing JP XIII was developed to help ensure an efficient measure of disintegration time [11]. In this method, a camera is interfaced along a path of disintegration with a personal computer and a motion sensor to help monitor all movements. Thereafter, CCD camera records disintegration course while transferring pictures to a computer for analysis and calculation of actual disintegration time [11].

Texture analyzer (TA)

Through a TA process, a new operating structure is developed and designed like a human oral system through which attached granules are systematically eliminated during disintegration process. It is a process of measuring disintegration time of RDTs in an artificial environment similar to oral cavity [14]. In texture analyzer method, RDT is placed on a grid and lowered into a disintegration medium by a trigger force that pushes it down a disintegration medium [14]. Effect of changing medium and temperature is assessed during evaluation. An increase in temperature and nature of medium affect disintegration time of RDTs as observed by use of artificial saliva and distilled water mediums [14]. Quantitative values are calculated through disintegration profile of RDTs with measurements of starting time being recorded as T1 and end process time recorded as T2. Values gained through TA aid in obtaining RDT profiles in addition to identifying an excellent correlation with *in-vivo* disintegration time in a patient's mouth. This process is largely applauded for its high accuracy level that enables it to provide a mouth-feel of RDT as it establishes thickness of tablets with disintegration distance obtained from their profiles [14]. It is also advantageous as it allows for differentiation of various rapidly disintegrating tablets through their various characteristics as outlined in their profiles. However, it is difficult to always construct accurate equipment with exact standard measurements. So, disintegration time of these tablets using TA is very short, making it difficult to give an accurate measure of disintegration time using a stopwatch.

The Novel disintegration apparatus (Rotary Shaft)

It is simpler to ascertain disintegration time of various RDT formulations using this disintegration-time device [15]. This approach is faster compared to other conventional approaches. The method involves use of a rotating shaft that has a weight of about 10 g and a speed of rotation of about 10 rpm. It employs use of tablets stored in both severe conditions and appropriate conditions of about 37 oC. Disintegration time of tablets obtained using this method provides values similar to those of human sensory tests conducted in the oral cavity involving saliva and tongue pressure towards the upper mouth palate [15]. This test is advantageous because it provides accurate results that directly correlate to what exactly happens to RDTs in human oral cavity [16]. The approach is difficult to use for precise observations because it is impossible to witness the mechanism that causes pill disintegration. The same test was adopted in another study in which direct compression orally

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disintegrating tablets were applied in an apparatus set that provides different volumes of purified water as dissolution medium in different temperatures [17]. However, the provision of magnetic resonance imaging (MRI) helps in providing an analysis of the properties of disintegrating tablets, helps to determine exact disintegration time, and improves quality of tested results as well as mechanism of disintegration process. With this apparatus, it is easier to determine effect of compression force, temperature, and volume of medium in enhancing disintegration [17]. This method has the challenge of requiring extremely high attention levels.

Prototypical disintegration tester (PDT)

The prototypical disintegration tester (PDT) measures *in-vitro* disintegration time for ODTs with high accuracy [13]. To help achieve more advanced results, this disintegration method employs use of a CCD camera to monitor behaviour and reaction mechanisms of ODT profiles. Furthermore, CCD camera attached to this method helps enhance accurate determination of reaction end-time. With this process, water absorption rate of ODTs is measured in an artificial environmental set-up with a commercial tester, and an estimation of disintegration time was measured. Using swelling and water absorption rate, this method is used to accurately determine disintegration time of ODT with an additional enhancement of a CCD camera [13]. The method is particularly helpful since it provides a precise estimation of disintegration time and aids in describing disintegrating behaviour. Difficulty in creating the test apparatus is a major draw-back [13].

Novel method using commercial RDTs

The novel method of measuring disintegration time is an advancement of conventional method described in Japanese Pharmacopoeia (JP) XIII [18]. Many studies were done to determine disintegration time associated with rapidly disintegrating tablets, *in vitro* using this new and simple method while comparing it with conventional disintegration test in JP XII which is inefficient due to its environmental conditions that largely differ from those in oral cavity, and with human sensory test [19]. New method involves use of suspension meshes kept at room temperature sandwiching the RDT with some additional weight exerted to facilitate disintegration process. A drop of test fluid, which is either purified water or artificial saliva induces wetting for disintegration to commence. This process equally takes a relatively short time, comparable to that taken by healthy volunteers, which means that this new method is most likely efficient and reliable [18].

Conventional method on the other hand utilizes a large amount of water that is not present in oral cavity with no associated pressure associated resulting in a slow disintegration time. Novel method incorporates main factors that facilitate disintegration, which include volume of oral saliva and internal pressure that pushes against the mouth palate [18]. Thus, novel method offers special benefits such as ease of construction, adjustable oral cavity environment, and ease of measuring at least two aspects of tablets. Furthermore, medium in this method impinges on the tablet drop by drop and also only from topside, which makes it unreliable and does not reflect *in vivo* disintegration time.

wetting test

Wetting test is a commonly used method of assessing disintegration time of orally disintegrating tablets (ODTs) [8]. This test involves immersing samples of ODTs in an appropriate amount of water and recording disintegration time. Amount of water used in wetting test experiment is assumed equivalent to that in human oral cavity. In a previous analysis, most studies noted that wetting test experiments failed to show exact oral cavity environment [8]. Water absorption ratio while determining disintegration rate was calculated to improve accuracy of these results. However, another study found that even though certain tablets will swell after absorbing water and fail to disintegrate, it may be possible to estimate disintegration time by wetting test [8]. This, therefore, was a major challenge of wetting test experiment, hence, allowing for use of a more effective and innovative method, which is the shaking bath test method [8]. With this method, all types of ODT tablets are effectively measured and exact disintegration time are recorded. Enhanced shaking test, which improved upon the previous wetting test method, allowed for measurement of disintegration times rather than water permeation times. The only difficulty is that water absorption ratios are not measured.

Table 1: Methods for measuring disintegration time

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Method	Advantages	Disadvantages
Basket rack assembly (USP)	It allows for physical observation of the disintegration process in addition to allowing multiple experimental performances to help determine actual disintegration pace.	It is a confused process.
Novel method utilizi ng CCD camera	Outlines RDTs morphological changes during disintegration process and enhances accuracy and quality of monitoring disintegration time.	It is difficult to construct an efficient CCD camera accommodating apparatus.
Texture analyzer (TA)	It allows for differentiation of various RDTs.	Complexity to construct an apparatus with exact standard measurements.
Novel disintegration apparatus	It is accurate in measuring disintegration time, ability to determine effect of compression force, temperature, and volume of medium enhancing disintegration process	Requires a lot of attention.
Prototypical disintegration tester (PDT)	It provides accurate results that are directly correlated to in vivo disintegration in oral cavity and, also ability to determine disintegrating mechanisms.	Developing test apparatus is considered a complex process.
Novel and simple method	Easier to construct, adjustable oral cavity environment and also measures various aspects of ODTs	Disintegration time strongly depends on available oral cavity environment and conditions that are difficult to measure.
OD-Mate Testing	It is very accurate as evidenced by strong correlation of results between artificial taste sensors and gustatory sensation testing techniques.	Weight above tablet is very high and there is no rotary shaft or pressure to enhance disintegration process.
Modified Wetting Test	Disintegration time of all ODTs is effectively measured	Inability to measure water absorption ratio of ODTs.

Standardized wetness shake tests are highly effective in determining times at which different ODTs disintegrate, providing more accurate results [8]. The methods presented with their characteristic advantages that enable efficient estimation of disintegration time are shown in Table 1.

CONCLUDING REMARKS

Introduction of ODTs has solved some problems associated with drug administration to pediatric and elderly patients, who account for a sizable proportion of world's population. Number of companies in ODT drug delivery market is high, as evidenced by an ever increasing number of patents and marketed products. Among other drug delivery companies, those in ODT sector have a huge potential for extending product self-life and increasing profitability of existing pharmaceuticals. This delivery facilitates a very short disintegration time. Because disintegration time is an essential parameter for ODT development, regular USP disintegration test is not suitable. All of the studies developed are evidence that there is a variety of effective methods to evaluate disintegration time and mechanisms. It is therefore an expectation that future trends in drug delivery innovation will continue to bring together different disciplines to create novel technologies.

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