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REVIEW ARTICLE

Advantages and Quality Control of Orally Disintegrating Tablets

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Summary

Orally disintegrating tablets (ODTs) are most preferred and accepted solid dosage forms by the patients. These tablets disintegrate in the saliva in the mouth within a short period of time and offer an advantage for populations who have difficulty in swallowing. Quality control of orally disintegrating tablets can be done by friability, porosity, hardness, wetting time, water absorption capacity, in vitro disintegration test and dissolution test. This article summarizes advantages and in vitro quality control tests of orally disintegrated tablets.

Key Words: *Orally disintegrating tablets, advantages, quality control.*

Ağızda Dağılan Tabletlerin Üstünlükleri ve Kalite Kontrollü

Özet

Ağızda dağılan tabletler hastalar tarafından en çok tercih edilen ve kabul edilen katı dozaj formlarıdır. Bu tabletler ağızda tükrükte kısa sürede dağılır ve yutma güçlüğü çeken kişiler için avantaj sağlar. Ağızda dağılan tabletlerin kalite kontrolleri, friabilite, porozite, sertlik, ıslanma zamanı, su absorpsiyon kapasitesi, in vitro dağılma zamanı ve çözünme testleri ile yapılabilir. Bu makale ağızda dağılan tabletlerin avantajlarını ve kalite kontrollerini özetlemektedir.

Anahtar Kelimeler: *Ağızda dağılan tabletler, avantajları, kalite kontrol.*

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INTRODUCTION

Drug delivery through oral route is the most preferred and accepted way of application by the patients. Solid dosage forms in the shape of tablets used orally have the most substantial and significant place among the entire pharmaceutical formulations (1). Over the last 30 years, orally disintegrating tablets (ODTs) are gaining considerable importance. These tablets disperse in the saliva in the mouth within a short period of time. Saliva containing the dispersed drug is then swallowed through the oesophagus (2).

In the European Pharmacopeia, orally disintegrating tablets are specified as "orodispersible tablets" and defined as "orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed"(3) while in the United States Food and Drug Administration (FDA) Regulation (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research), they are classified as "orally disintegrating tablets" and defined as "A solid dosage form containing medicinal

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substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" (4).

Advantages of Orally Disintegrating Tablets

In addition to having the advantages of conventional tablet dosage forms, ODT formulations are easy to swallow like the liquid dosage forms and superior to the oral liquid dosage forms since the dosage can be adjusted more correctly(5). Owing to their solid dosage forms, they have a better stability, an easier production process, smaller packing size and they are more convenient for the use of the patients (2,5-7). Their pleasant taste (palatability) is among the advantages of these dosage forms in comparison to the other conventional tablets or capsules. Of the dosage forms that have been developed to improve the patient compliance, effervescent tablets and dry powder suspensions need to be prepared before application while gums or chewing tablets have such disadvantage that the aged patients are usually not able to chew large pieces, and as for the medicine that remain in the mouth for a longer period of time, they can leave an unpleasant or bitter taste sometimes (8). Since the ODTs are designed to disperse or dissolve at once when they contact saliva, it is not necessary to chew the tablet or drink water to swallow the entire tablet. Advantages like comfort and increase in patient compliance can be gained with application of orally disintegrating tablets to patients such as the aged, paralyzed and bedridden ones who are not able to swallow as well as to the pediatric, geriatric and psychiatric patients who refuse to swallow (9,10). Most of the patients experience difficulty in swallowing tablets and hard gelatinous capsules, as a result of which, they fail to take their medicine as prescribed. It is reported that swallowing difficulty (dysphasia) that can be observed due to neoplasia, neuromuscular and metabolic disorders, infectious diseases, iatrogenic causes, anatomic abnormalities, autoimmune disorders and reasons such as stress/anxiety has been observed widespread throughout the entire age groups and that 35% of the overall population has been affected (11).

Patient noncompliance to therapy and especially the schizophrenic patients' refraining from swallowing their medicine by hiding conventional tablets under their tongues is a frequently experienced situation in psychiatry. It is evident that the patients' comfort and quality of life will be increased by means of the rapid ODT technology used in psychiatry (12). Estimates have been reported that 50% of the population has been affected by this problem which results in ineffective therapy and patient noncompliance to therapy (2, 8). Orally disintegrating tablets are preferred especially by children and aged people as well as the patients who wish to take their medicine at any time comfortably. In addition, rapid disintegration of tablets may cause rapid dissolution and absorption and thus may cause the medicine to show its effect rapidly (13). It is stated that the actual purpose in development of formulations for some orally disintegrating tablets is to increase bioavailability in comparison to conventional tablets (14). It is also reported that some formulations containing rapidly dissolved active substances may be subject to pre-gastric (oral, pharyngeal, esophageal) absorption because they are dispersed in saliva in the oral cavity. Buccal, pharyngeal and gastric areas are the site of absorption for most of the formulations (2). It is reported that the medicine subject to pre-gastric absorption may demonstrate increased bioavailability when formulated as orally disintegrating tablets (15). Pre-gastric absorption also prevents the first-pass effect and provides a significant advantage for the drug subject to hepatic metabolism. It is reported that selegiline containing orally disintegrating tablets are dissolved orally within seconds, that they pass directly to systemic circulation by means of trans-buccal absorption and are therefore protected from metabolization and that their bioavailability is increased in comparison with conventional tablets (16). Orally disintegrating tablet formulations also provide advantages in the industrial field such as diversity of products and extension of patent time (17).

In spite of these advantages, orally disintegrating tablets are sensitive to temperature and humidity (5). It is difficult to prepare active substances of high dosage like antibiotics in the orally disintegrating tablet form (18). Besides, patients on anticholinergic medicine or those suffering from dry mouth due to decreased saliva production may also not be suitable for using ODT (18).

Preparation Methods

In general, freeze-drying (lyophilization), molding and direct compression technologies are used extensively in preparation of orally disintegrating tablets (10, 19).

ODT preparation methods also include sublimation, spray-drying, cotton-candy process, phase transition, three dimensional printing and mass extrusion (19, 20).

In vitro Characterization Studies of ODTs

Tablet Breaking Resistance and Friability

Tablet breaking resistance is determined by means of a hardness assessment device used to measure the force required to break the tablets under certain conditions (3, 21-25). Tablet friability device is made up of polished transparent synthetic polymer inside with an apparent diameter and depth. Accurately weighed tablets are placed in this plastic chambered friabilator and rotated at 25 rpm/ min for 4 min. After 100 rotations, tablets are taken out, their powder is removed and they are weighed again In general, friability is required to remain below 1%. For hygroscopic tablets, it is necessary to work in a humidity controlled environment (3).

These tests are more convenient for the tablets prepared by means of molding or direct compressing methods. Molded tablets are usually prepared with compressing force less than conventional tablets (8, 26). These tests cannot be applied to ODTs prepared by means of the lyophilization method as they are very fragile. In the lyophilization method, the active substance is dissolved or dispersed in a vehicle/polymer aqueous solution (26, 27). After being poured into blister pockets, it is frozen under liquid nitrogen and following lyophilization, blister is closed.

Porosity Measurement

As tablet porosity relatively indicates degree of water penetration to formulation, therefore, it is relevant to disintegration time. ODT porosity measurement can be conducted using a mercury porosimeter (23, 28-30).

The porosity ($\in$) can also be calculated based on actual density of tablet (ρ_{actual}) determined by means of a pycnometer, mass (m) and volume (V) measured (31-34), using the following equation.

$$(\in) = 1-[m/ (\rho_{actual}*V)]$$

Porosities of ODTs prepared by means of spray-drying, lyophilization, sublimation and cotton-candy methods are more in comparison with those prepared by means of other methods. In the spray-drying method, aqueous mixture containing excipient is spray-dried to obtain a highly porous structure, active substance is added to this porous powder mixture and tablet is then compressed (26,35). In the sublimation method, inert solid materials (such as urea and camphor) that are rapidly sublimated are mixed with other tablet excipients and the mixture is compressed as tablet, sublimated material is then disassociated by sublimation to obtain tablet with porous structure (36, 37). In the cotton-candy method, the polysaccharide or saccharides make up the matrix called floss by rapid melting and rotation. Tablets prepared by means of this process are highly porous and they leave a nice taste in the mouth because of rapid dispersion of sugar with saliva (26).

Dissolution Test

Usually USP Apparatus II (paddle) method and 50 rpm of paddle speed are recommended for the ODT dissolution test. However, a better discrimination between in vitro dissolution profiles can be made at low paddle speeds. Additionally, it has been reported that when the basket method is used, pieces of tablet from its rapid dispersion may accumulate at the inner top side of the basket and may not mix up adequately and hence reproducible results may not be obtained (38,39).

Determination of Water Absorption Capacity/ Wetting Time

In this test, a circular tissue paper is placed in a petridish and tablet is placed on the paper. A certain volume of distilled water is added, and the time required to cover the entire tablet surface is recorded as the wetting time (29-31, 40).

As for the water absorption capacity, ODT is first weighed when dry (W_{first}) and after it has become entirely wet, it is weighed again (W_{last}), and water absorption capacity is calculated using the equation given below (29, 30).

$$\text{Water Absorption Capacity} = 100(W_{last}-W_{first})/W_{first}$$

Determination of ODT Disintegration Time

ODTs must be hard enough to withstand the mechanics of production, storage and transportation yet must be sufficiently friable to dissolve or disperse to small pieces for the patient to swallow comfortably (41). Determination of disintegration time is important for the development of ODT formulation.

1. In Vivo Determination of Disintegration Time

In vivo determination of disintegration time may be carried out with healthy volunteers picked up on a random basis. After tablet is put on the tongue, the period of time until disintegration of the last granule will be measured. It is recommended that the volunteers should wash their mouths at the end of the test. The requirement for permission from the Board of Ethics and application of tablets that contain active substances which have many side effects on healthy volunteers are the restrictions of this test (29, 30, 42-47).

2. In Vitro Determination Methods of Disintegration Time

2.1. European Pharmacopeia (EP 6.0)

It is specified in the European Pharmacopeia (EP 6.0) that disintegration time for orodispersed tablets is the same with that for the conventional uncoated tablets and that the samples should be dispersed within less than three minutes (3).

2.2. Determination of Disintegration Time with Modified Dissolution Test Device

USP Apparatus II method at 100 rpm of paddle speed in 900 mL of distilled water (37°C) has been used in this test (29, 30). Tablet is placed in a sinker, which is then suspended in the middle of a glass container, and dispersion time is determined as the period of time the tablet has been disintegrated entirely and has passed through sieve of the sinker to the modified dissolution test apparatus. Que et al. prepared rizatriptan benzoate containing ODTs and used the modified dissolution test device. They found that the paddle stirring rate, diameter of the sinker sieve and tablet hardness were effective on disintegration time, whereas, temperature of dispersion medium and position of the sinker were not very effective on disintegration time and this method was well correlated with in vivo disintegration time at a mixing speed of 50 rpm (48).

2.3. Texture Analysis Method

In this method, texture analysis device is used in order to determine the beginning and ending points of disintegration. Tablet adhered under a probe is pressed by means of applying a stable pressure towards base of the beaker containing distilled water and extent of penetration is measured. As the tablet begins to disperse, probe functions at a certain distance to gain a stable force and extent of compression increases. Beginning and ending time of disintegration is determined from the time-extent graphics composed by the device (42, 49).

2.4. CCD Camera Method

In this method, disintegration device is made up of a steel disintegration container which has 200 mL distilled water at a temperature of 37 ± 2°C and an external container with thermostat containing water. Images taken by the CCD camera during the period of disintegration are transferred to a computer. Disintegration time is calculated using the graphics obtained with regard to the wear on the tablet surface area as a function of time (50).

2.5. Rotary Shaft Method

In this method, ODT is placed on a perforated plate and pressure is applied by means of the rotary shaft used to produce a mechanical stress on the tablet. Located at the tip of the rotary shaft weight is a sponge circled with a conducting material. As the weight contacts the plate, the moment when disintegration ends will be determined by means of an electrical sensor (51, 52).

Conclusion

ODTs are more widely accepted solid dosage forms in the recent years. They can be easily used like the liquid dosage forms and superior to the other tablets. The dosage can be adjusted more correctly and they are widely preferred by the patients. Quality control of ODTs is also very important since these tablets require special attention during their formulation. Therefore, development of new advanced control and formulation techniques are necessary to improve the quality of the ODTs.

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