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Review

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Mouth Dissolving Tablets II: An Overview of Evaluation Techniques

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Abstract

Mouth dissolving tablets are well established dosage forms available in the market. The numerous advantages that they offer to the patients in terms of compliance as well as to the manufacturers in terms of huge revenues by line extension of products are well known. In spite of such popularity, there seems to be lack of a standardized system to characterize these dosage forms. Enormous work has been done in this field, wherein some of the researchers have developed their own methods of evaluation.

This article attempts to present a detailed review regarding technological advances made so far in the area of evaluation of mouth dissolving tablets with respect to special characteristics of these unique dosage forms. In the absence of any available standardized method, the author's recommendation on critical issues in the field may be considered.

Keywords

Mouth dissolving • Evaluation technique • Disintegration test • Taste masking • E-tongue

Introduction

Mouth dissolving drug delivery systems (MDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. MDDDS offer the luxury of much more accurate dosing than the primary alternative, oral liquids. This segment of formulation is especially

designed for dysphagic, geriatric, pediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations [1–3]. As they dissolve/disintegrate very fast when placed in the mouth, MDDDS are the most convenient dosage forms for dysphagic, pediatric and geriatric patients with swallowing problem. They do not require water for administration, thus are good alternative for travellers and for bed ridden patients. They simply vanish when placed in the mouth, so cannot be hidden in mouth by psychotic patients. These products not only increase the patient's compliance but also fetch large revenues to manufacturers due to line extension of the existing formulation.

In the recent past, several new advanced technologies have been introduced for the formulation of mouth dissolving tablets (MDTs) with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients. The technologies utilized for fabrication of MDDDS include lyophilization [4], moulding [5], direct compression [6], cotton candy process [7], spray drying [8], sublimation [9], mass extrusion [10], nanonization [11] and quick dissolve film formation [12]. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability.

Although, numerous technologies had been developed for the fabrication of these uniques dosage forms in last two decades, but so far, no standardized technique has been designed or mentioned in pharmacopoeias for their evaluation except in European Pharmacopoeia (EP), which defines orodispersible tablets as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed". EP also specifies that the orodispersible tablets should disintegrate within 3 minutes when subjected to conventional disintegration test used for tablets and capsules [13]. This article presents a detailed review regarding the evaluation measures available in literature to characterize the MDTs, which have been designed keeping in view the special features of these novel drug delivery systems.

Evaluation of Mouth Dissolving Tablets

Measurement of Tablet Tensile Strength

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using equation I:

Eq. I. $T = 2F / \pi dt$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively [14].

Though, this is a widely used and accepted method for hardness testing, it is not applicable to very delicate tablets prepared by lyophilization technique wherein the liquid suspension of drug and excipients is freeze dried in the blister pocket and the dried tablets are finally sealed in the blister. Special aluminum (alu) blisters with peel off blister covers are used as packaging material for these tablets. Flashdose tablets prepared by cotton candy process are also poor candidates for this test [15, 16]. This test is best suited for tablets prepared by direct compression and moulding methods. However, the tensile strength of these tablets is always kept low which needs to be compromised to keep the disintegration time as minimum as possible.

Friability

The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for MDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is again not applicable for lyophilized and flashdose tablets, but is always recommended for tablets prepared by direct compression and moulding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

Moisture Uptake Study

MDTs usually contain high concentration of hydrophilic excipients with the minimum possible hardness which together contribute to their increased susceptibility to moisture uptake. In order to maintain their physical integrity and surface texture, special attention is required during the storage and packaging of these dosage forms. Therefore, moisture uptake studies are strongly recommended for MDTs. The test can be carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37 °C for 24 hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the dessicator for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing. The materials with high moisture resistant properties should be used for packaging for e.g. alu strip pack, alu-alu blister or polyethylene sealing on blister. The use of appropriate quantity of desiccant in HDPE bottle packs with minimum head space is highly recommended to ensure stability of the product during its shelf life [17].

Measurement of Tablet Porosity

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration. This instrument is based on the capillary rise phenomenon wherein an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure difference across the interface is given by the Washburn equation II, where the pressure drop is inversely related to the pore size (perpendicular radius) [18].

Eq. II. $\Delta P = -(2\gamma/r) \cos \theta$

where γ is the surface tension of the liquid, r is the perpendicular radius and θ is the angle of contact between the liquid and the capillary walls. Pore radius is calculated from eq II using experimental data obtained in the form of P. In this test, the contact angle between mercury and the tablet is kept at 140° and the surface tension at the interface of mercury and the tablet is 0.486 N/m. Pore sizes in the range of 0.06–360 μm, can be efficiently measured by this technique [19, 20].

Otherwise, the tablet porosity (ε) can also be calculated using equation III:

Eq. III. $\varepsilon = 1\text{-}m / (\rho_t V)$

Where ρ_t is the true density, and m and V are the weight and volume of the tablet, respectively [14]. Tablets prepared by spray drying, lyophilization and cotton candy process generally possess high porosity and therefore, have extremely low disintegration time.

Wetting Time and Water Absorption Ratio

A study [20] on wetting time and water absorption ratio reported the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R, was determined according to equation IV:

Eq. IV. $R = 100\ (W_a - W_b)/W_b$

Where W_b and W_a are the weights of tablet before and after water absorption, respectively.

Fineness of Dispersion

This is a qualitative test specified by EP for dispersible tablets [13]. We recommend performing this test on tablets which are not truly mouth dissolving, but are fast oral disintegrating tablets (ODTs). It is an assessment of the grittiness which arises due to disintegration of the tablet into coarse particles. The test is performed by placing two tablets in 100 ml water and stirring it gently, till the tablets get completely disintegrated. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μm without leaving any residue on the mesh.

Disintegration Time

The methods for evaluation of in-vivo disintegration time had been explained in literature [9, 21, 22]. However, the results from this type of test typically reveal unsatisfactory reproducibility and are not reliable as the difference in disintegration time is few seconds in most cases. In addition, the in-vivo disintegration test has its own limitation of issues related to ethics and the safety of the volunteers. At present, the disintegration time of MDTs is measured using the disintegration test for conventional tablets that is described in the Pharmacopoeias. EP has set the limit of 3 mins for disintegration time of MDTs using conventional disintegration apparatus. However, no special apparatus is mentioned in the

pharmacopoeias for disintegration test of MDTs and the conventional method available seems to be inappropriate for MDTs. This is because of the extreme operating conditions in the disintegration apparatus which fails to provide a significant discrimination among the rapidly disintegrating tablets. Furthermore, the conventional test employs a relatively huge volume of test solution (900 ml) compared to the volume of saliva in human buccal cavity, which is less than 6 ml. Therefore, the results obtained from the conventional disintegration test do not reflect the actual disintegration rate in the human mouth which usually ranges from 5–30 secs [9, 21, 22]. To overcome these issues, several new methods have been proposed, which are reviewed here.

Disintegration Test using Modified Dissolution Apparatus

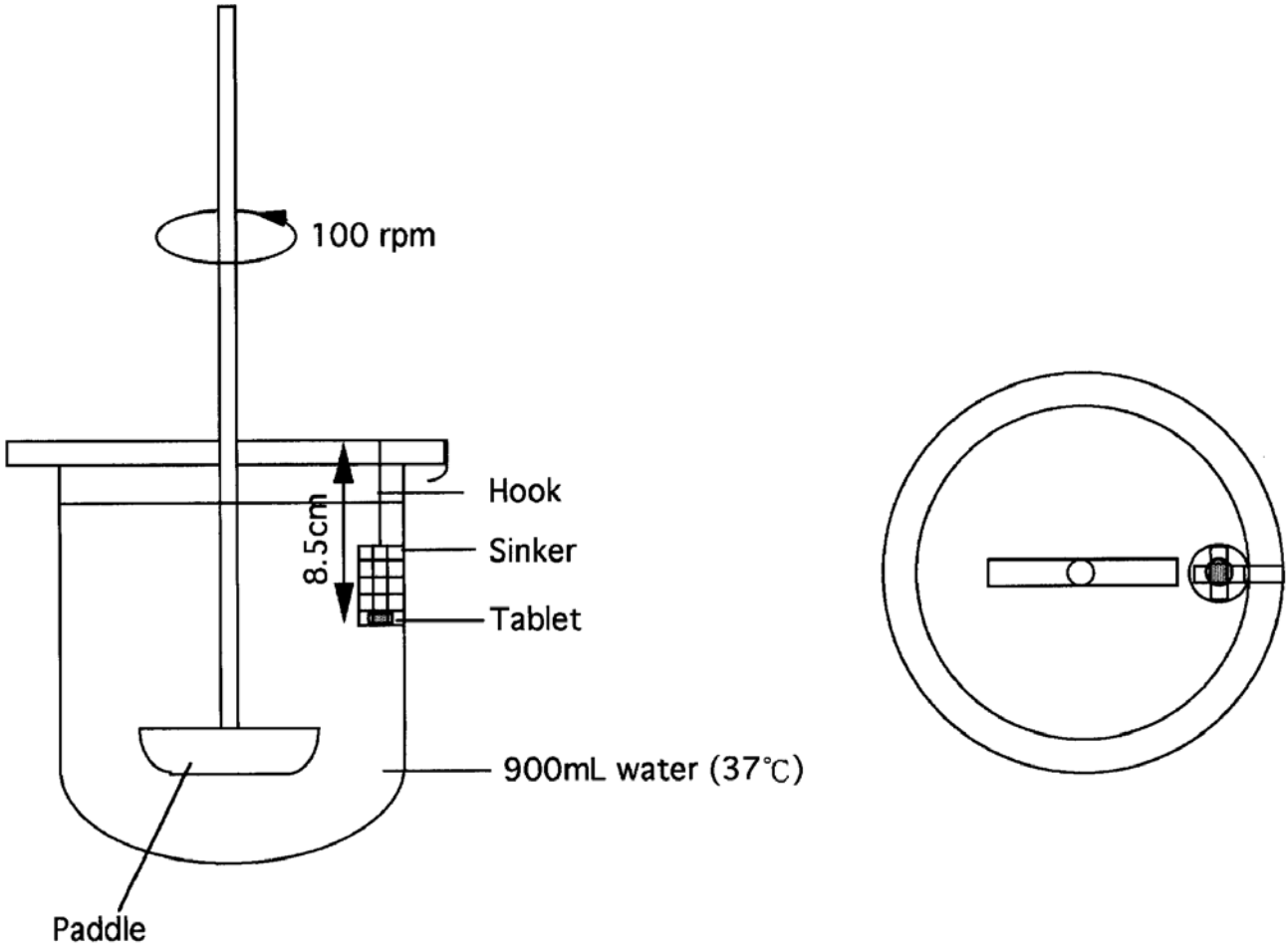

Fig.1. Schematic view of modified dissolution apparatus for disintegration test (from reference [21])

Bi et al., [21] suggested the use of a modified dissolution apparatus, instead of the disintegration apparatus as shown in Fig.1. In this experiment, 900 ml of water maintained at 37 °C as the disintegration fluid and a paddle at 100 rpm as stirring element were used. Disintegration time was noted when the tablet disintegrated and passed completely through the screen of the sinker (3–3.5 mm in height and 3.5–4 mm in width, immersed at a depth of 8.5 cm from the top with the help of a hook). This method was useful in

providing discrimination among batches which was not possible with the conventional disintegration apparatus.

Disintegration Test on Wire Cloth

Motohiro et al., [23] carried out disintegration test by placing the MDT on a wire cloth No. 10 and dropped water on it at a rate of 4 ml/min. The time required by the tablet to completely pass through the wire cloth was noted as disintegration time.

Disintegration Test with CCD Camera

Morita et al., [24] developed a sophisticated disintegrating test apparatus equipped with a CCD camera. This apparatus is divided into two distinct sections, a disintegration component and a measurement device. The mode of measurement involves the continuous monitoring and recording of disintegration time course by obtaining pictures through the CCD camera, which are simultaneously transferred into a computer and stored. The speciality of this apparatus lies in the combination of detailed pictures obtained by the CCD camera and the calculation capabilities of the computer.

The disintegration apparatus consists of a plastic cell partitioned into two parts: one component comprises of an inner tank containing the stirring bar, the grid fabricated from stainless-steel and 200 ml of distilled water as disintegration medium maintained at 37±2 °C; the second component is an outer tank, which functions as a water bath heated at 37±1 °C (Fig. 2a) via circulation of thermostated water. The grid consists of three hollow areas, equidistant from the center, in which the tablets are positioned using a support to avoid their displacement during the test (Fig. 2b).

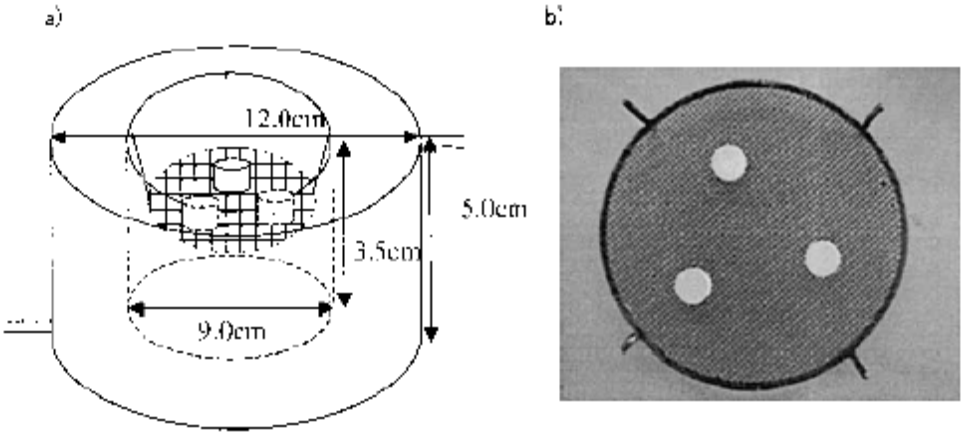

Fig.2. Plastic Disintegration Cell (a) and Tablet Support Grid with Three RDT (b) (from reference [24])

The measurement apparatus consists of a CCD camera and a computer. The CCD camera is positioned in such a manner that the top surface of the three tablets can be seen on the camera's screen. The disintegration time course can be analyzed graphically with the data obtained using this equipment. It is especially useful for very fast dissolving tablets prepared by lyophilization which have disintegration time of less than 10 secs.

However, this method has a limitation of absence of any mechanical stress, as the MDT placed in the oral cavity receives some mechanical stress produced by the tongue.

Disintegration Test on Shaking Water Bath

Fu et al., [25] conducted the disintegration test by placing the MDT in a glass cylinder fitted with 10 mesh at its base. This set up was further placed in a shaking water bath operated at 150 rpm. 1 ml of purified water maintained at 37 °C temperature was used as medium. The critical parameters of this method were the operational speed of shaking water bath and volume of the medium.

Disintegration Test with Rotary Shaft Method

In another study, Narazaki et al., [22] proposed a better disintegration method for MDTs as shown in Fig. 3(a). In the experimental method, the MDT was placed on the wire gauze (D), slightly immersed in the medium, and then compressed by a rotary shaft (E) which was employed to provide mechanical stress on the tablet by means of its rotation and weight. Purified water at temperature 37 °C was used as the medium. The critical parameters of the proposed method were the rotation speed and the mechanical stress. Using this new method, it would be possible to predict a more realistic disintegration rate in human. The compression force can be easily adjusted using the weight (A). The rotary shaft crushes the MDT which disintegrates into the medium. The endpoint was measured visually using a stopwatch.

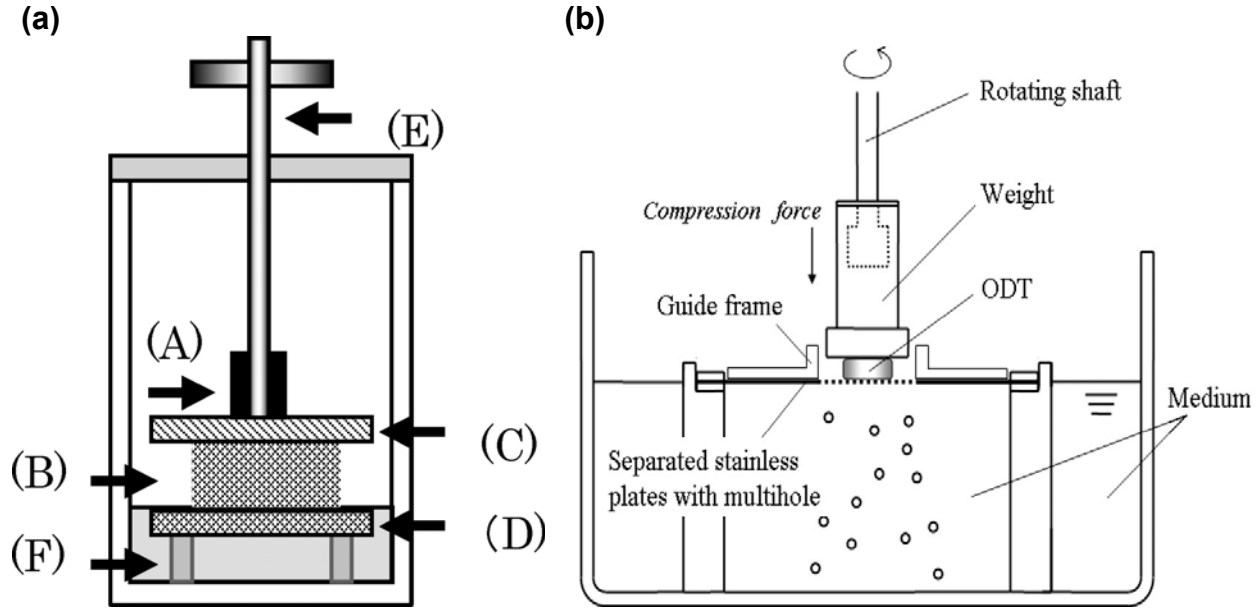

Fig.3. (a) Apparatus of rotary shaft method for MDT (A) weight, (B) MDT, (C) wetting sponge, (D) wire gauze, (E) rotary shaft, (F) medium. (b) improved rotary shaft apparatus (From reference [22, 26])

The above mentioned apparatus was modified by Harada et al., [26] by placing a sponge at the surface of shaft weight to increase friction with the MDT (Fig. 3b). Therefore, the weight transmits the torque of the rotating shaft to the ODT and grinds it on the stainless steel perforated plate which is used in place of wire gauge. The electrodes are attached on

each side of the plate. The rotation speed and weight were optimized to set the mechanical pressure. When the weight makes contact with separated plates, the electric sensor conveys a signal that indicates the end point of the disintegration test of the ODT.

Disintegration Test using Texture Analyzer [27, 28]

In another study, a texture analysis apparatus was used to measure the start and end time points of tablet disintegration [27]. The set up is shown in Fig. 4. A constant penetration force was applied to tablets via a cylindrical flat-ended probe. The tablet, under constant force, is immersed in a defined volume of distilled water and the time is plotted against the distance, which the probe travelled into the tablet. Typical time–distance profiles, generated by the texture-analysis software, enabled the calculation of the starting and ending time of disintegration.

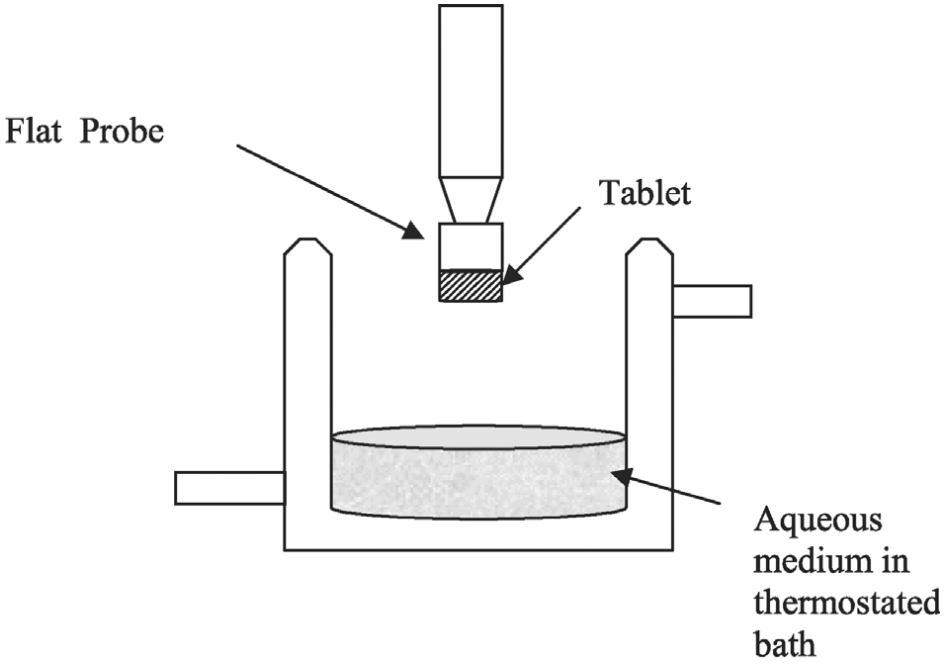

Fig. 4. Texture analyzer apparatus for disintegration test (from reference [27])

Disintegration Test using ElectroForce® 3100

An instrument "ElectroForce® 3100" has recently been designed by the Bose corporation with an objective to simulate the disintegration condition of the MDTs in mouth. It is based on application of low force to measure small displacements and disintegration rate as a function of manufacturing process of a variety of MDTs (Fig.5).

The instrument typically consists of a lower plate to hold the tablet on which a force of about 10 mN is applied followed by addition of approximately 5 ml of water maintained at 37 °C. It has the advantage of providing better resolution than those available instruments with moderate to high force test [29]. This is the first equipment of its type which is available in the market for evaluation of ODT. This tabletop system can be used by the manufacturers and regulatory agencies to monitor and evaluate the different fabrication technologies of MDTs.

Some of these new methods have been able to produce satisfactory discrimination between tablets of different types and could perhaps be taken into consideration as an effective method for evaluation of disintegration time of MDTs.

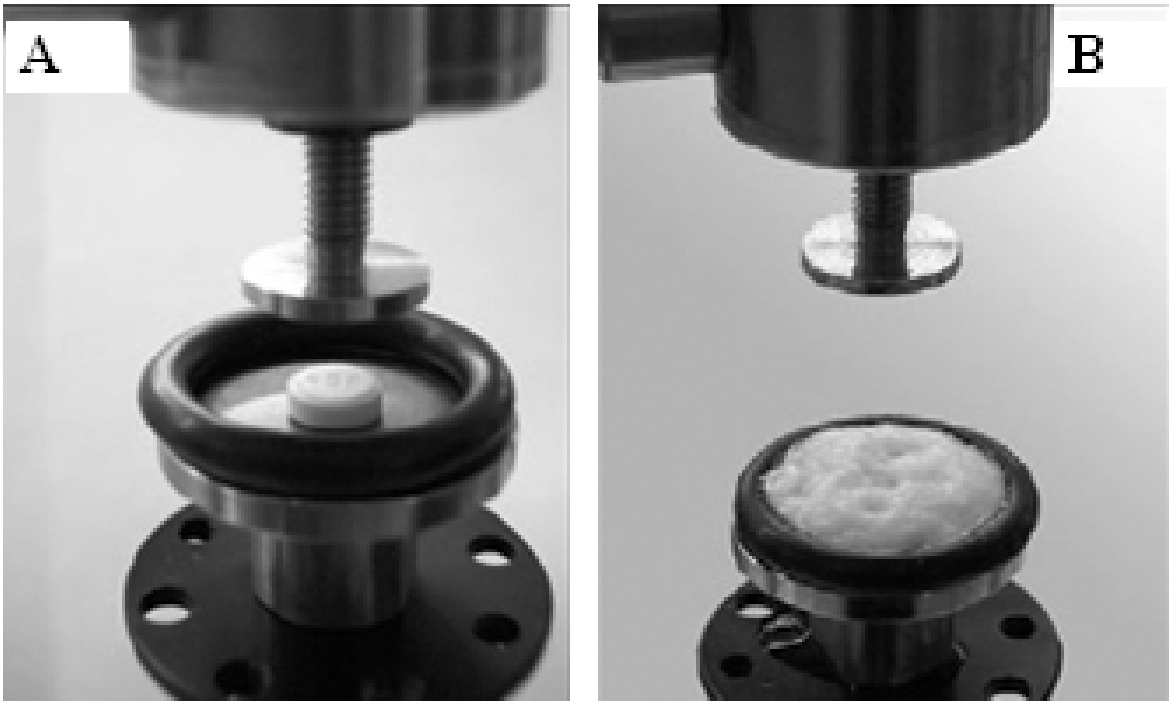

Fig.5. ElectroForce® apparatus for Disintegration test A. ODT mounted on test plate before loading. B. ODT after completion of Disintegration test (from reference [29])

Dissolution Testing of Mouth Dissolving Tablets

The conventional method of dissolution could be extended to in-vitro evaluation of MDT [30]. The dissolution conditions for the reference listed drugs available in USP can be utilized for preliminary in-vitro studies to mimic better in-vivo conditions. Apart from the above, multimedia dissolution studies in various buffer solutions of different pH viz. 0.1 N HCl; pH 4.5 and 6.8 buffers should be carried out for interpretation of their in-vivo performance and pharmaceutical equivalence. USP apparatus II (paddle) with a speed of 50 rpm seems to be most suitable and common choice with appropriate dissolution media volume to maintain sink condition. Typically, the dissolution of MDTs is very fast when using USP monograph conditions and therefore, under such conditions the dosage forms behave almost equally. Hence, slower paddle speeds may be employed to obtain a profile and better discrimination among various batches prepared during the developmental stage. In case of tablets approaching or exceeding one gram weight and containing relatively dense insoluble particles, there are the chances of heap formation at the bottom of the dissolution vessel. Under such a condition, although the tablet disintegrates completely, there is a significant reduction in the apparent dissolution rate. However, this issue can be resolved by using higher paddle speed of 75 rpm [31]. The USP I (basket) apparatus may have application for certain MDTs which disintegrate into particles with floating tendency. However, tablet fragments or disintegrated tablet masses may become

trapped on the inner top side of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. In that case, a higher basket rotation speed of 100 rpm is recommended for quality assurance purpose while the formulation should be evaluated on the basis of a separate discriminatory disintegration test as listed above.

Dissolution Test for MDTs with Taste-Masking Approaches

Drug substances with bitter or objectionable taste in any orally-administered dosage form, including suspensions and chewable tablets are required to be suitably taste masked. The taste masking of the dosage form may be carried out using multiple approaches including use of taste masking flavors and sweetners, pH dependent/independent polymer coating of drug particles or complexation using ion exchange resins or cyclodextrins. Though the use of flavors and sweetners do not require special attention, the other taste-masking approaches greatly influence dissolution method development, specifications and testing. In such cases, the pH of the dissolution media plays a vital role in either the dissolution of the pH sensitive polymer or the release of the drug from the ionic complexes. Coated drug microparticles for controlled-release purpose, where bitter taste of drug is automatically masked, can also be incorporated in MDTs. Here, the in-vitro dissolution study condition would be similar to that for a controlled release dosage form along with a discriminatory disintegration test to evaluate the disintegrating properties of the system.

The disintegration time of MDT in a dissolution vessel is generally less than thirty seconds and therefore, is not an important factor in the resulting dissolution profile in terms of discrimination. Thus, the in-vitro dissolution study is carried out to assure the complete release of the drug in the media within the stipulated time period. Based on the functionality of the dosage form, single point dissolution is sufficient for an immediate release dosage form while a multi point dissolution profile is required for the evaluation of a controlled release system. However, it is important to observe the tablet's disintegration pattern and behavior of the disintegrated particles during the dissolution test for a better understanding of the role of the excipients that are used for the purpose [31].

Evaluation of Effectiveness of Taste Masking

The formulation's organoleptic properties like taste, mouth-feel and appearance are of considerable importance in differentiating products in the market and can ultimately determine the success of a product. The following discussion is focused on the in-vitro and in-vivo methods for evaluation of the taste masking property.

In-vivo Method

The in-vivo taste evaluation consists of a double blind crossover study, carried out on a trained taste panel of healthy volunteers with sound organoleptic senses, with their prior consent. On placing the dosage form in the oral cavity, the disintegration time is noted after which it is further held in mouth for 60 sec by each volunteer, and the bitterness level is recorded against pure drug (control) using a numerical scale. After 60 sec, the disintegrated tablet is spitted out and the mouth is rinsed thoroughly with mineral water. The numerical scale bears the following values: 0 = tasteless, 0.5 =aftertaste, 1.0 = slight, 1.5 = slight to moderate, 2.0 = moderate, 2.5 = moderate to strong, 3 = strong and 3+ = very strong [32]. Alongwith the taste evaluation, a simultaneous observation of mouth feel

(grittiness or smoothness) should also be noted to assess the quality of the product. This pharmaceutical taste assessment typically requires a large, trained taste panel and sophisticated interpretation. The tests may require the similar health safeguards as for a clinical trial especially for potent drugs like steroids and antipsychotics. Overall, a properly conducted taste trial adds huge investment of time and money to the product development process. Therefore, a well designed in-vitro taste masking evaluation technique would be a valuable alternative.

In-vitro Method

The conventional in-vitro method of dissolution study lacks relevance to simulate the behavior of an MDT in the buccal cavity, due to excessively large dissolution media volume. Therefore, a more relevant method was developed in our laboratory wherein 5 ml of pH 6.8 phosphate buffer (to simulate salivary pH and volume) was used to study the taste masking efficiency of risperidone resinate complex [33]. Risperidone resinate equivalent to 4mg of risperidone was placed in two 25 ml glass bottles. 5 ml of the buffer solution was then added and the bottles were allowed to stand for 60 sec and 120 sec, respectively. After the specified time, the suspensions were filtered using 0.45 µ nylon filters. The filtrates were analyzed for drug content. The test was performed in triplicate. It was found that 2.5% of drug was released in 120 secs. The bitterness threshold of risperidone is 25 µg/ml [34], while the concentration of the drug released in our study [33] was 20 µg/ml in 120 secs which is insufficient to impart bitterness. Moreover, the disintegration time of the prepared MDT was 20 secs which would be an added advantage in further reducing the release of drug in the oral cavity. However, a very fast drug release was observed in 500 ml of 0.1N HCl using USP dissolution apparatus II at 50 rpm (about 92% of drug released in 5 mins) [33].

The pharmaceutical taste assessment usually demands large panels and elaborate analysis, raises safety and scheduling issues, and can be time consuming and expensive. These challenges were overcome with the invention of a breakthrough electronic sensor array technology, the “E-tongue”. This is a sensor device for recognition (identification, classification, and discrimination), quantitative multicomponent analysis and artificial assessment of taste and flavor. This unique device helps to considerably reduce the developmental time and costs, subjectivity, bias and safety concerns. The E-tongue mimics the three levels of biological taste recognition: the receptor level (taste buds in humans, probe membranes in the E-tongue); the circuit level (neural transmission in humans, transducer in the E-tongue) and the perceptual level (cognition in the thalamus in humans, computer and statistical analysis in the E-tongue). At the receptor level, the E-tongue uses a seven-sensor probe assembly to detect the dissolved organic and inorganic compounds. The probes consist of a silicon transistor with proprietary organic coatings, which govern the probe’s sensitivity and selectivity. Measurement is done potentiometrically. Each probe is cross-selective to allow coverage of full taste profile. At the circuit level, the system samples, quantifies and records potentiometer readings. At the perceptual level, taste cognition happens in the computer, whereas the E-tongue’s statistical software interprets the sensor data into taste patterns. Depending on the study design, data analysis can produce a variety of informations.This electronic sensor was employed for taste optimization of MDT prepared by lyophilization process (Zydis technology) by Cardinal Health [35].

Conclusion

Extensive work had been carried out till date in order to evaluate the MDTs and among them, many are proved to have significant discriminatory power. However, the final selection of an appropriate evaluation method depends on the consideration of the manufacturing technology, taste masking approach employed and the excipients used in the product development process. Despite the fact that a lot of these dosage forms are available in the market, still a lot of work needs to be done to standardize the evaluation techniques and streamline the regulatory issues. Apart from all, application of electronic sensor array – "E-tongue" and ElectroForce® Disintegration tester seem to have a bright future ahead in the area of MDTs evaluation.

Authors' Statement

Competing Interests

The authors declare no conflict of interest.

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