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REVIEW ARTICLE

IN-VITRO AND *IN-VIVO* CHARACTERIZATION OF MOUTH DISSOLVING TABLET: AN UPDATED REVIEW

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ABSTRACT

Mouth dissolving tablets (MDTs) has extended much attention as a preferred alternative to conventional oral dosage form. It provides an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. MDTs have the unique property of rapidly disintegrating and/ or dissolving or releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. The current review describes the ideal characteristics, significance, limitations and mainly lays emphasis on the *in-vitro* and *in-vivo* characterization of MDT.

Keywords: Mouth dissolving tablets, disintegration, *in-vivo* and *in-vitro* evaluation, dysphagia.

INTRODUCTION

MDTs are also called as orally disintegrating tablets, orodispersible tablets, fast dissolving tablets, rapid dissolving tablets, rapid disintegrating tablets, porous tablets and rapi melts.[1] Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients.[2] Oral routes of drug administration have world wide acceptance up to 50-60% of total dosage forms.[3] However, tablets are most favorite and popular among the currently used dosage forms and efficacy of these dosage forms have been clinically evaluated because of its convenience in terms of self medication, compactness, ease in manufacturing, pain avoidance, and versatility.[4-7] It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications.[8,9] To avert the problems associated with conventional dosage forms, MDTs have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and travelling patients.[10-13] For these reason, scientists have developed the innovative concept of Mouth Dissolving Drug Delivery System (MDDDS) emerged from the desire to provide patient with more conventional means of taking their medications. MDDDS have started gaining popularity and acceptance as new drug delivery systems. These tablets disintegrate into smaller granules or melts in the mouth from a hard solid to a gel like structure, allowing easy swallowing by patients. The disintegration time for good MDTs varies from several seconds to about a minute.[14] United States Food and Drug Administration(US FDA) defined MDTs as "A solid dosage form containing medicinal substance or active pharmaceutical ingredients(API) which disintegrates rapidly usually within seconds when placed upon the tongue[15].

The basic approach in development of MDT is the use of superdisintegrants like crospovidone, croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate etc. as synthetic superdisintegrants in the formulation of MDTs, which provide instantaneous disintegration of tablet after keeping on tongue, their by release the drug in saliva.[16] The proper selection of disintegrant or superdisintegrant and its consistency of performance are of critical importance in formulation development of such tablets.[17] Various technologies used for manufacturing MDTs include freeze drying, spray drying, tablet molding, sublimation, direct compression, sugar-based excipients, and disintegrant addition.[18] Recent market studies indicate that ore than half of the patient population prefer MDTs to other dosage forms such as regular tablets or liquids (>80%).[19] Furthermore, market size and popularity of these dosage forms will surely expand in future. This article is emphasized on the *in-vivo* and *in-vitro* evaluation of MDTs along with ideal properties, significance, and limitations of MDTs.

IDEAL CHARACTERISTICS OF MDTS

MDTs have several ideal characteristics to distinguish them from the more traditional dosage forms.[20-28] These tablets should:

- Not require water or other liquid to swallow.
- Give good mouth feel.
- Easily Dissolve/Disperse/Disintegrate in saliva within few seconds.
- Have a satisfactory taste masking properties.
- Cost effectiveness.
- Show signs of low sensitivity to environmental conditions like temperature, humidity etc.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration.
- Allow the manufacture of tablet using conventional processing and packaging equipments.

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- Allow high drug loading.
- Be portable without fragility concerns.

SIGNIFICANCE OF MDTS

MDTs offer all advantages of solid dosage forms and liquid dosage forms along with special advantages[1,29-42] which include:

- Improved compliance/added convenience.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down.
- Rapid drug therapy intervention.
- Good mouth feel property helps to change the perception of medication as "bitter pill" particularly in pediatric patients.
- Risk of chocking or suffocation during oral administration is avoided, thus providing improved safety.
- No water needed.
- No chewing needed.
- Improved stability.
- No special set up required for the industry.
- Rapid onset of action.
- Lower doses.
- New business opportunities like product differentiation, line extension, and life-cycle management, exclusivity of product promotion and patent-life extension.
- Accurate dosing.
- Small packaging size.

LIMITATIONS OF MDTS

The factors responsible for limiting their use vary from formulation till the effect of drug in the body.[10,43-45] These are:

- MDTs usually have inadequate mechanical strength. Hence, vigilant handling is required during formulation process.
- The tablets may leave disagreeable taste and/or grittiness in mouth if not formulated appropriately.
- Drugs with larger doses are difficult to formulate into MDTs e.g. Rifampin (600mg), ethambutol (1000mg) etc.
- Taste masking is required.
- Proteinaceous drugs should be avoided, if co-administration of enzyme inhibitors such as aprotinin, bestatin, puromicin and bile salts are required for the inhibition of proteolytic enzymes present in saliva.
- Patients who concomitantly take anticholinergic medication may not be the best candidates for MDTs and patients like Sjogren's syndrome or dryness of the mouth due to decrease saliva production may not be good candidates for these tablet formulation.

IN-VITRO CHARACTERIZATION OF MDTS

Enormous work has been done in this field, wherein some of the researchers have developed their own methods of evaluation. In the recent past, several new advanced technologies have been introduced for the formulation of MDTs. To ensure drug release from MDTs, the dosage form requires thorough and meticulous evaluation for optimum performance, which can be assessed indirectly by *in-vitro* technologies.

Evaluation of tablets

Evaluation parameters of tablets mentioned in the pharmacopoeias used to be assessed, along with some special tests are discussed.[33] These include: organoleptic evaluation, weight variation, thickness, hardness, friability, wetting time, water absorption ratio, *in-vitro* disintegration test, drug content uniformity, swelling index, *in-vitro* drug release studies and moisture uptake studies.

Organoleptic properties

This is essential step in case of most oral formulation due to more residence time in the oral cavity. General appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.[24,34,48] *In-vitro* methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. Experiments using electronic tongue measurements are reported to distinguish between the sweetness levels in taste-masking formulation.

Weight variation

Twenty tablets are selected at a random from each formulation and average weight is determined. Then individual tablets are weighed using digital electronic balance and the individual weight is compared with the average weight. The mean ± SD (standard deviation) values are calculated.[49] The weight variation test would be a satisfactory method of assessing the drug content uniformity.

Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting. Three tablets are taken randomly from each formulation and their thickness is measured with Vernier caliper. The mean ± SD values are calculated.[34,49]

Hardness

Hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. Hardness of the tablets is measured using Pfizer type hardness tester. Three tablets are selected from each formulation randomly and their hardness is measured. The resistance of the tablet to abrasion, chipping or breakage under conditions of storage and handling before usage depends on its hardness. The mean ± SD of hardness values are calculated. It is expressed in Kg/pound.[50,51]

Friability

Friability of the tablets is determined using Roche friabilator. This device subjects a number of tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at

distance of six inches with each revolution. Preweighed sample of tablets is placed in the fribilator and are subjected to 100 revolutions.[52,53] Tablets are then de-dusted and reweighed and percentage of weight loss is calculated by the formula:

$$Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Wetting time

Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a piece of tissue paper folded twice is placed in a small petridish (i.d. 6.5 cm) containing 6 ml of water. A tablet is kept on the paper nd the time for complete wetting is measured. The mean ± SD values are calculated.[54,19]

Water absorption ratio

The weight of the tablet prior to placement in the petridish is noted (w_b) utilizing a digital balance. The wetted tablet is removed and reweighed (w_a). Water absorption ratio, R is then determined according to the following equation:

$$R = 100 \times (w_a - w_b) / w_b$$

Where, w_b and w_a are tablet weights before and after water absorption, respectively. The mean ± SD values are calculated.[49,55,56]

In vitro disintegration test

Disintegration time is very important for MDTs which is desired to be less than 60 seconds for MDTs. This rapid disintegration assists swallowing of the tablet and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. *In-vitro* disintegration time is determined using disintegration test apparatus (Electrolab, USP model ED-2L) without disk for six tablets. The disintegration medium is 900 ml of distilled water kept at 37 ± 0.5ºC and stirred at a rate of 30 ± 2 cycles/min. The time is measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. The test is carried out in triplicate.[57,58]

Drug content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual dosage form.[1] Limit of content uniformity is 85-115%.

Swelling index

The swelling index is the volume in milliliters occupied by 1 gram of a superdisintegrant, including any adhering superdisintegrant, after it is swollen in an aqueous liquid for 4 h. In a 25 ml ground-glass stoppered cylinder graduated over a height of 125 ± 5 mm in 0.5 ml divisions, 1.0 g of superdisintegrant is placed. Unless otherwise directed, the superdisintegrant is moistened with 1.0 ml of alcohol, 25 ml water is added and close the cylinder. The cylinder is shaken vigorously every 10 min for 1 h. It is allowed to stand for 3 h. At 90 min after the beginning of the test, any large volume of liquid retained in the layer of the superdisintegrant and any particle of superdisintegrant floating at the surface of liquid is released by rotating the cylinder about a vertical axis. The volume occupied by the superdisintegrant is measured, including any adhering mucilage. Three tests are carried out at the same time. The swelling index is calculated by the means of three tests.[16,59,60]

***In-Vitro* drug release studies**

The expansion of dissolution methods for MDTs is comparable to the approach taken for conventional tablets, and is practically indistinguishable. Media such as 0.1N HCL and buffers (ph – 4.5 and 6.8) should be evaluated for MDT much in the same way as their ordinary tablet counter parts. The USP 2 Paddle apparatus is used for this purpose which is the most suitable and common choice for MDTs, with a paddle speed of 50 rpm commonly used.[61] Typically the dissolution of MDT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to attain a profile. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles.

Moisture uptake studies

This parameter should be conducted for MDTs to assess the stability of the dosage form. Ten tablets from each batch are kept in a desiccator over calcium chloride at 37^0C for 24h. The tablets are weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity is attained by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrants) is kept to check the moisture uptake by the other excipients. Tablets are weighed and the percentage increase in the weight is recorded. If the moisture uptake tendency of a weighed tablet is high, it requires special dehumidified area for manufacturing and packaging.[44,62-65] 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 High density polyethylene bottle packs with minimum head space is highly recommended to ensure stability of the product during its shelf life.

IN-VIVO CHARACTERIZATION OF MDTS

In-vivo studies exhibit the actual action of MDT in the oral-oesophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. *In-vivo* test for the determination of disintegration time of MDTs can be conducted on volunteers who are usually randomized to receive the treatments and then directed to clean their mouth with water. Tablets are placed on their tongues, and the time for disintegration is measured by immediately starting a stopwatch. Immediately after the last noticeable granule has disintegrated, the stopwatch is stopped and the time recorded.[66-68] *In-vivo* taste evaluation consists of a double blind crossover study, carried out on a trained panel of healthy volunteers with their prior assent. On keeping 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 noted down against pure drug (control) using a numerical scale. The numerical scale bears the following value: 0 = tasteless,

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0.5 = after taste, 1.0 = slight, 1.5 = slight to moderate, 2.0 = moderate, 2.5 = moderate to strong, 3 = strong and 3+ = very strong. A few examples are illustrated below, showing the work of various scientists in the field of *in-vivo* evaluation.

Panizo C *et al.*, (2010) studied *in-vivo* immunological changes induced by a short course of grass Allergy Immunotherapy Tablets (AIT). They performed a randomized, double-blind placebo-controlled trial with 78 patients randomly assigned to receive either grass AIT or placebo in a 2:1 ratio and found that treatment with grass AIT for grass pollen allergic rhinoconjunctivitis induces immunological changes after only 1 month of treatment.[69] **Visser MR *et al.*, (2010)** adopted Inulin solid dispersion technology to improve the absorption of the BCS class IV drug TMC240. Single-dose study in dogs (200mg of TMC240), plasma concentrations of TMC240 remained below the lower limit of quantification (<1.00ng/mL) in all animals (n=3 per tested formulation), except in one dog receiving the inulin solid dispersion tablet [C (max) =1.8ng/mL, AUC (0-7h) =3.0ngh/mL]. The current data demonstrate that a solid dispersion of TMC240 in an inulin matrix allows considerable improvement in the release of poorly water-soluble TMC240, both *in-vitro* in the presence of a surfactant and *in-vivo* upon oral administration.[70] **Indumathi D *et al.*, (2010)** investigated *in-vivo* release studies of fluxetine fast dissolving tablet as control formulation and test formulation using rabbit as animal model. The plasma samples were separated by centrifugation and the drug was extracted. Then the samples were assayed by high performance liquid chromatography.[71] They found that *in-vivo* drug release studies of test formulation were found to be better than that of control formulation. **Gupta AK *et al.*, (2011)** carried out *in-vivo* mouth disintegration test for determination of disintegration time in saliva. They found that with increases in camphor ratio, tablet disintegrates rapidly in the saliva, which may be related to an improvement of the water penetration into the tablets due to high porosity.[72]

CONCLUSION

With the increase demand of novel drug delivery, the MDDDS has become one of the major mile stone of current investigations. This article attempts to present a detailed review regarding technological advances made so far in the area of evaluation of MDTs with respect to special characteristics of these inimitable dosage forms. Encouraging results of *in-vivo* evaluation revealed that in future, MDT may be most acceptable and prescribed dosage form due to its immediate action (within minute). Their characteristic advantages such as administration without water, anywhere, anytime lead to their increased patient compliance in today's scenario of hectic life.

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