INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)
Platform for Pharmaceutical Researches & Innovative Ideas
www.ijprd.com

[Review Article]

AN APPROACH FOR RAPID DISINTEGRATING TABLET: A REVIEW

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ABSTRACT

Over the past three decades, rapid disintegrating tablets have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. Generally, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Rapid disintegrating drug delivery systems may offer a solution for these problems. Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance.

Rapid disintegrating tablets (RDT) are useful in patients, such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup, leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attack, or coughing for those who have an active life style. The objective of this article is to review the development of RDTs, challenges in formulation, new RDT technologies and evaluation methodologies, suitability of drug candidates, and future prospects.

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Key Words
Rapid disintegrating tablet, Enhanced bioavailability, Superdisintegrants, Rapid disintegrating technologies, Evaluation.

INTRODUCTION

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance.

Definition

The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." A rapid dissolving tablet can be defined as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for rapid dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet.

A Rapid disintegrating drug delivery system, in most cases, is a tablet that dissolves or disintrigrants in the oral cavity without the need of water or chewing. Most rapid-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble exipients. These are also called melt-in-mouth tablets, repimelts, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets.[1]

The concept of rapid dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets; hard gelatine capsules particularly in pediatric and geriatric patients. Such problems can be resolved by means of Rapid Dissolving Tablets. Rapid dissolving tablets are meant to disintegrate immediately upon contact with the saliva leading to rapider release of the drugs in the oral cavity and disintegrate rapidly within 15 seconds to 3 minutes. There are two different types of dispersible tablets which have to be distinguished: one dosage form disintegrates instantaneously in the mouth and to be swallowed without a need of drinking water and second the tablet formulation readily dispersed in water to form dispersion, easy to ingest by the patient. Rapider the drug in solution, quicker the absorption and onset of clinical effect, due to absorption from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [2]. Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, orally disintegrating tablets 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. The advantages of this new type of solid dosage form are widely recognized, since the term ''oro-dispersible tablet" appears in the European Pharmacopoeia defined as ''uncovered tablet for buccal cavity, where it disperses before ingestion". These tablets display a rapid and spontaneous de-aggregation in the mouth, soon after the contact with saliva, though they can be handled or extracted from the package without alteration. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption to fulfil these requirements, tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid deaggregation of the matrix. Different technological techniques, such as freeze drying or moulding or direct compression are currently employed to prepare the formulations of this type present on the pharmaceutical market[3]. Developing a solid oral dosage form in today's market can be challenging. There are many pressures to discover new entities and maximize the lifecycle of products while

maintaining safety, cost-effectiveness, and speed to market. Tablets are almost certainly the most cost-effective and efficient form of dispensing medicine. The main purpose to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance[4]. Dispersible tablets disintegrate either rapidly in water, to form a stabilized suspension, so, it's preferred for patients who cannot swallow a solid dosage form and the API is unstable if formulated in liquid formulation. It is also helpful for patients having prolonged illness
who are prone to nauseatic sensations if they have to swallow a tablet. The added advantage of this formulation is rapider onset of action as compared to standard compressed tablet[5]. The properties of the water dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity after dispersion are necessary to investigate during manufacturing which decides the product performance[6]. The aim of this study was to formulate RDTs with sufficient mechanical integrity and to achieve rapider disintegration in the oral cavity without water. To achieve this goal, diluents and sweetening agent for the formulation of tablets. Attempts were made to enhance dissolution rate along with rapider disintegration using superdisintegrants in the formulation of tablets[7]. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion). The dissolution of a drug can also be influenced by disintegration time of the tablets. Rapider disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and rapider dissolution[8]. The maincriterion for rapid-disintegrating tablets is the capacity to disintegrate or dissolve rapidly in oral cavity with assessment of saliva within a minute without need of water. Thereafter this could enhance the bioavailability of drug through pregastric absorption from the mouth, pharynx and esophagus[9].

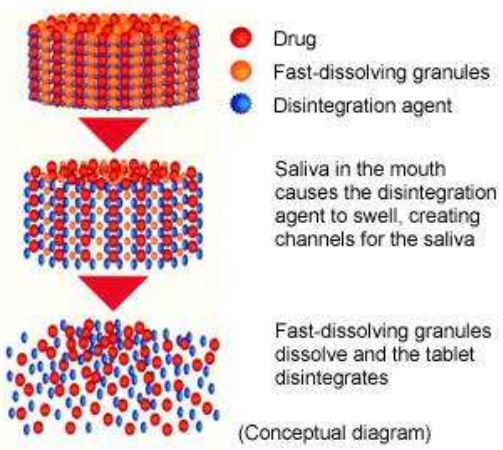

Fig no: - 01. Conceptual diagram of RDT

Rapid-dispersing formulations, commonly called rapid-melting tablets (RMTs), also offer advantages over other dosage forms such as effervescent tablets, extemporary suspensions, chewing gum, or chewable tablets, which are commonly used to enhance patient compliance. Effervescent tablets and extemporary suspensions require preparatory steps before administration of the drug. The elderly, who often are unable to chew large pieces of gum or tablets, sometimes experience unpleasant taste problems when bitter drugs are present. In this case, the bitterness of the chewable tablets markedly increases because of the prolonged time that they are in the mouth or as a result of leaching of the drug from chewed or broken microcapsules.

Biopharmaceutical Consideration[10]

When new drug delivery system put on, it is must that to consider Biopharmaceutical factor like metabolism and excretion.

Pharmacokinetics:

In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution while RDT is rapidly disintegrates in oral cavity and dissolution is rapid. Due to disintegration of RDT in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders

may be considered as separate unique Medicare population. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. In geriatric patients, decrease in body mass and total body water result in decreased volume of distribution of water-soluble drugs and increased volume of distribution (Vd) of lipid soluble drugs.

Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamic:

Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.

- Decreased ability of the body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- Decreased sensitivity of the CVS to b-adrenergic agonist and antagonist.Immunity is less and taken into consideration while administered antibiotics.
- Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.
- Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.

Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patient.

Salient Features of Rapid Disintegrating Drug Delivery System[11]

- Ease of administration to patients who refuse to swallow a tablet, such as paediatric and geriatric patients and, psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feels properly of MDDS helps to change the basic view of medication as "bitter pill", particularly for paediatric patients.
- Rapid dissolution of drug and absorption which may produce rapid, onset of action.
- Some drugs are absorbed from the month pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

Advantages of RDT[12]

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

Formulation Aspects in Developing RDT

Rapid disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the RDTs formed vary in various properties such as,

- Mechanical strength of tablets
- Taste and mouth feel
- Swallowability
- Drug dissolution in saliva
- Bioavailability
- Stability

TECHNOLOGIES AND EVALUATION

Technologies employed for preparation of RDT[13]

Various technologies, detailed below are commonly applied for the production of rapid disintegrating systems. They are Freeze-drying or lyophilisation, Sublimation, Spray drying, Moulding, Mass extrusion, and direct compression.

(1) Freeze-drying[14, 15, 16]**:** Freeze-drying (lyophilization) is a process in which water is sublimated from the product after freezing. The main advantage being that pharmaceutical substances can be processed at nonelevated temperatures, thereby eliminating adverse thermal effects, and stored in a dry state with relatively few shelf-life stability problems. Freeze-dried forms offer more-rapid dissolution times than other available solid products. The lyophilization process imparts a glassy amorphous structure to the bulking agents and, sometimes, to the drug, thereby enhancing the dissolution characteristics of the formulation. The use of freeze-drying, however, is strongly limited by the time and handling required for processing, the limited amount of materials processed for each batch, and the high cost of the equipment and processing. Other major disadvantages of the final dosage forms include the lack of physical resistance in standard blister packs and their limi-ted ability to accommodate adequate concentrations of active.

(2)Disintegrant Addition[17] **:** Disintegrant addition technique is one popular technique for formulating Rapid-dissolving tablets because of its easy implementation and cost-effectiveness. The basic principle involved in formulating Rapid-dissolving tablets by disintegrant addition technique is addition of superdisintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel.

Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 – 9.1 to prepare rapid dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Rapidly disintegrating tablets of bitter drugs oxybutynin & pirenzepine were prepared by using the taste masked granules and h mixture of exicipients consisting of crystalline cellulose (Avicel PH 02) and low-substituted hydroxypropy cellulose HPC, LH-11), Ishikawa et al. prepared rapidly disintegrating tablets using microcrystalline cellulose (Avicel PH-M series) that was spherical and had a very small particle size 7-32 µm). Instead of conventional microcrystalline cellulose (PH 102). Tablets prepared using microcrystalline cellulose; PH-M06 and L-HPC in the ratio of 9:1 were very rapidly disintegrating) in saliva. They concluded that Avicel PH-M06 was superior to Avicel PH 102 in terms of the feeling of roughness in the mouth. Rapid dissolving table of efavirenz (anti HIV agent) were formulated by using combination of microcrystalline cellulose and sodium starch glycolate as super disintegrant. Gillis et al, prepared a rapid-dissolving tablet of galanthamine hydrobromide which comprises of spray dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, a cross linked polymeric disintegrant such as cross povidone and with a direct compression process of preparing such rapid-dissolving tablets. Rapid-dissolving tablets having analgesic activity was formulated using a combination of superdisintegrants. Rapid oral disintegration tablets were developed by direct compression using co-ground mixture of D-mannitol and crospovidone. CIMA labs patented Orasolv technology by employing the evolution of carbon dioxide or the effervescence as disintegration mechanism in the formulation of rapid-dissolving tablets. The OraSolv technology is an oral dosage form, which combines taste-masked drug ingredients with a

quick dissolving effervescent excipient system. Taste masking is achieved through a process of microencapsulation, which coats or entraps the active compound in an immediate release matrix. The effervescent excipient system aids in rapid disintegration of the tablet, permitting swallowing of pharmaceutical ingredients before they come in contact with the taste bud. The Orodispersible tablet dissolves quickly without chewing or without water and allows for effective taste masking of a wide variety of active drug ingredients, both prescription and non-prescription. Flashtab technology™ is a patented technology of Prographarm, which employ combination of taste-masked multiparticulate active drug substances, a disintegrating agent, a swelling agent and other excipients to form a multiparticulate tablet that disintegrates rapidly. Rapidly disintegrating multiparticulate tablet was prepared by using taste-masked microcrystals of drugs, crosslinked disintegrating agent and soluble diluent with binding properties.

Milind P Wagh et al[18] prepared FDT by direct compression method after incorporating superdisintegrants croscarmellose sodium, crospovidone and sodium starch glycolate. Nine formulation having superdisintegrant at different concentration (10, 15, 20 mg) level were prepared. Effect of superdisintegrant on wetting time, dispersion time, drug content and *in vitro* release has been studied. Tablet containing cross carmellose sodium showed xcellent *in vitro* dispersion time and drug release as compared to other formulation. After study of nine formulations F3 shows short dispersion time with maximum drug release in 30 min. It is concluded that rapid-dispersible aceclofenac tablets could be prepared by direct compression. using superdisintegrants.

(3) Moulding[19] : Moulding process includes moistening, dissolving, or dispersing the drug with a solvent then moulding the moist mixture into tablets (compression moulding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution, or suspension at ambient pressure (no vacuum lyophilisation), respectively. The moulded tablets formed by compression moulding are air-dried. As the compression force employed is lower than conventional tablets, the moulded tablet results in highly porous structure, which increases the disintegration and dissolution rate of the product. However, to further improve dissolution rate of the product powder mixture should be sieved through very fine screen. As moulding process is employed usually with soluble ingredients (saccharides) which offers improved mouth feel and disintegration of tablets. However, moulded tablets have low mechanical strength, which results in erosion and breakage during handling**.** Different moulding techniques can be used to prepare mouth-dissolving tablets:

a. Compression moulding: The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

b. Heat moulding: A molten matrix in which drug is dissolved or dispersed can be directly moulded into Mouth dissolving tablets.

c. No vacuum lyophilisation: This process involves evaporation of solvent from a drug solution or suspension at a standard pressure.

(4) Sublimation[20] : The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. Urea, ammonium carbonate, ammonium bicarbonate, h exa methelene tetramine, camphor etc.) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures. Additionally, several solvents (e.g. cyclohexane, benzene) can be also used as pore forming agents.

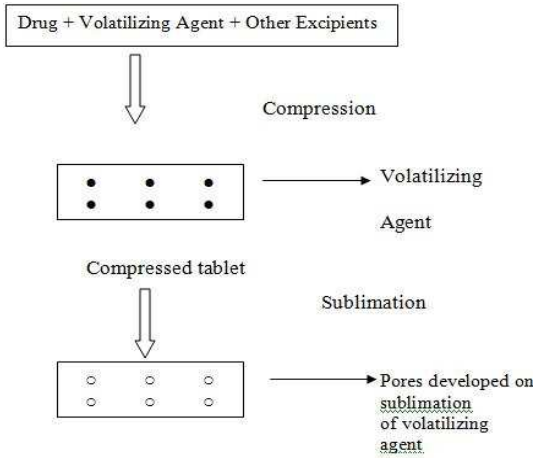

Fig no:-02 Sublimation method

(5) Spray-Drying : Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. I sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

(6) Mass-Extrusion[21] This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

(7) Direct compression : Direct compression is the easiest way to manufacture tablets and, therefore, FMTs. The great advantage of direct compression is the low manufacturing cost. It uses conventional equipment, commonly available excipients, and a limited number of process steps. Moreover, high doses can be accommodated in FMTs, the final weight of which can easily exceed that of other production methods. The direct-compression tablet's disintegration and solubilization are based on the single or combined action of disintegrants, water-soluble excipients, and effervescent agents. The disintegration time is, in general, satisfactory, although the disintegrating efficacy is strongly affected (and limited) by tablet size and hardness. Large, hard tablets can have a disintegration time greater than that usually required for FMTs.As a consequence, products with optimal disintegration properties often have a medium–small size (weight) and/or a low physical resistance (high friability and low hardness). Breakage of tablet edges during handling, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of the blister alveolus all result from insufficient physical resistance. In many cases, the disintegrants have a major role in the disintegration and dissolution process of FMTs made by direct compression. The choice of a suitable type and an optimal amount of disintegrants is paramount for ensuring a high disintegration rate.The addition of other formulation components such as watersoluble excipients or effervescent agents can further enhance dissolution or disintegration properties. The understanding of disintegrant properties and their effect on formulation has significantly advanced during the last few years, particularly regarding so-called super-disintegrants .

Sandeep B. Patil et al[22] prepared Olanzapine, quick dispersing tablets by direct compression method. Effect of super disintegrant crospovidone on wetting time, disintegration time, drug content and in vitro release have been studied. A 32 factorial design was employed in formulating a quick dispersible tablet. The selected independent variables crospovidone and hydroxypropylcellulose showed significant effect on dependent variables i.e. disintegration time and percent drug dissolved. Disintegration time and percent drug dissolved decreased with increase in the level of crospovidone. The similarity factor *f*2 was found to be 72.68 for the developed formulation indicating the release was similar to that of the marketed formulation.

Table 01: Advantages and Disadvantages of the different technologies for preparing rapidly disintegrating pharmaceutical forms.

Challenges in formulating Rapid disintegrating tablets[23]

Palatability: As most drugs are unpalatable, rapid disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

Mechanical strength: The major criteria for rapid dissolving tablets is to disintegrate in oral cavity is that they should be made of either very porous and soft-moulded matricesor compressed into tablets with very low compression force, which makes the tablets friable, brittle, difficult to handle and often requiring

specialized peel-off blister packing that may add to the cost.

Hygroscopicity: Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Amount of drug: The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a rapid-dissolving oral films or wafers.

Aqueous solubility: Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process.

Size of tablet: The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm.

Table 02: Some RDT patents

Table 01: Advantages and Disadvantages of the different technologies for preparing rapidly disintegrating pharmaceutical forms.

TECHNOLOGY	ADVANTAGES	DISADVANTAGES
Freeze-drying	Immediate dissolution (<5 s)	Very poor physical resistance High cost of production Low dose of water-soluble drugs
Moulding	Very rapid dissolution (5–15 s), High dose.	High cost of production Weak mechanical strength Possible limitations in stability.
Tabletting (standard)	Low cost of production, Use of standard equipment/materials, High dose Good physical resistance	Disintegration capacity markedly limit by the size and hardness of the tabletsed
Tabletting (effervescent)	Use of standard equipment High dose Good physical resistance Pleasant effervescent mouth feel	Operating in controlled low humidity Need of totally impermeable blister

Table 02: Some RDT patents

Technology	Basis	Patent owner
Zydis	Lyophilisation	R.P.Scherer Inc.
Quicksolv	Lyophilisation	Janseen Pharmaceutica
Lyoc	Lyophilisation	Farmlyoc
Rapid melt	Moulding	Élan Corp.
Ziplets	Moulding	Eurand
RapiTab	Compressed Tablets	Schwarz Pharma
Orasolv,Durasolv	Compressed Tablets	Cima Labs Inc
Flashtab	Multiparticulate Compressed Tablets	Ethypharm
WOWTAB	Compressed Moulded Tablet	Yamanouchi Pharma Technologies, Inc.
FlashDose	Cotton-candy process	Fuisz Technology Ltd.

***Evaluation of RDT*[24.25]**

Evaluation parameters of tablets mentioned in the pharmacopoeias need to be assessed, along with some special tests are discussed here.

General Appearance

The 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.

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table.

Table 03. Weight variation specification as per IP

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

Assay

Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100 mg drug was shaken with 100 ml of 0.1N Hydrochloric acid in 100 ml amber coloured volumetric flask and from this 10 ml was pipette out and then dilute up to 100 ml. From standard solution again 10 ml pipette out and diluted up to 100 ml in ml.

Hardness/crushing/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:

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

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively23. Though, this is a widely used and accepted method for hardness testing, it is not applicable to very delicate tablets prepared by Lyophilisation 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 aluminium blisters with peel off blister covers are used as packaging material for these tablets. Flash dose tablets prepared by cotton candy process are also poor candidates for this test19-20. 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

To achieve % friability within limits for an FDT is a challenge to the formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

Wetting time and water absorption ratio

Wetting time of dosage form is related with the contact angle. Wetting time of the FDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10-cm diameter. Ten milliliters of water-soluble dye (eosin) solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (W_b). The wetted tablet from the petridish is taken and reweighed (W_a). The water absorption ratio, *R* can be then determined according to the following equation, $R=100(W_a-W_b)/W_b$.

Moisture uptake studies

Moisture uptake studies for FDT should be conducted to assess the stability of the formulation. Ten tablets

from each formulation were kept in a desiccator over calcium chloride at 37°C for 24 h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrant) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Disintegration test

The time for disintegration of FDTs is generally <1 min and actual disintegration time that patient can experience ranges from 5 to 30 s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for FDT should mimic disintegration in mouth within salivary contents.

Dissolution test

The development of dissolution methods for FDTs is comparable to the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent FDT. Other media such as 0.1 N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for FDT much in the same way as conventional tablets.

USP dissolution apparatus 1 and 2 can be used. 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. Kancke proposed USP 2 Paddle apparatus, which is the most suitable and common choice for RDTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of RDT is very rapid when using USP monograph conditions; hence, slower paddle speeds may be utilized to obtain a profile.

The USP 2 Paddle apparatus at 50-100 rpm is suitable for dissolution testing of taste-masked drug as well. The media used for the taste-masked drug should match that of the finished product to maximize the value of the test. High-performance liquid chromatography (HPLC) is often required to analyze dissolution aliquots due to presence of UV absorbing components, specifically flavors and sweetener. Excipient to drug ratio may be higher since the formulation is designed to have good taste and mouth feel, decreasing the detection of the drug to background (excipient) in the UV spectrophotometer.

Stability studies

The stability of selected formulations was tested according to International Conference on Harmonization guidelines for zone III and IV. The formulations were stored at accelerated (40± 2 ^{o} /75±5% RH) and long-term (30±2 ^{o} /65±5% RH) test conditions in stability chambers (Lab-Care, India) for six months following open dish method . At the end of three months, tablets were tested for disintegration time, hardness friability, thickness, drug content and moisture uptake[26]

Measurement of tablet porosity

Tablet porosity (ε) is calculated using following Equation

$\varepsilon = 1 - m/\rho tV$

Where, ρt is the true density and *m* and *V* are the weight and the volume of the tablet, respectively.

Mercury penetration porosimeter (Amico, USA) was used for measurement of the pore volume distribution of tablet.

Measurement of the disintegration in the oral cavity

The time required for the complete disintegration in the oral cavity was collected from five healthy male volunteers, who were randomly administered five kinds of tablets at 1 h time intervals.

Evaluation of Effectiveness of Taste Masking[27]

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. Along with 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 . 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, while the concentration of the drug released in our study 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 rapid 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).

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 flavour. 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 Etongue 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 lyophilisation process (Zydis technology) by Cardinal Health.

Table 04: Some of Promising Drug Candidates for Mouth Dissolving Tablets[28]

Table 05: Marketed Rapid Dissolving Tablets in India

Table 04: Some of Promising Drug Candidates for Mouth Dissolving Tablets[28]

S. No.	Category	Examples
1	Antibacterial agents	- Ciprofloxacin, tetracycline, erythromycin, rifampicin, penicillin, doxycyclin, nalidixic acid, trimethoprim, sulphacetamide, sulphadiazine etc.
2.	Anthelmintics	- Albendazole, mebendazole, thiabendazole, livermectin, praziquantel, pyrantel embonate dichlorophen etc.
3.	Antidepressants	- Trimipramine maleate, nortriptyline HCl, trazodone HCl, amoxapine, mianserin HCl, etc.
4.	Antidiabetics	- Glibenclamide, glipizide, tolbutamide, tolazamide, gliclazide, chlorpropamide
5.	Analgesics/anti-inflammatory Agents-	Diclofenac sodium, ibuprofen, ketoprofen, mefenamic acid, oxyphenbutazone, indomethacin, piroxicam, phenylbutazone, etc
6.	Antihypertensives:	- Amlodipine, carvedilol, diltiazem, felodipine, minoxidil, nifedipine, prazosin HCl, nimodipine, terazosin HCl etc.
7.	Antiarrhythmics	- Disopyramide, quinidine sulphate, amiodarone HCl, etc.
8.	Antihistamines	- Acrivastine, cetrizine, cinnarizine, loratadine, fexofenadine, triprolidine,
9.	Anxiolytics, sedatives hypnotics & Neuroleptics	- Alprazolam, diazepam, clozapine, mylobarbitone, lorazepam, haloperidol, nitrazepam , midazolam phenobarbitone,thioridazine, oxazepam, etc.
10.	Diuretics	- Acetazolamide, clorthiazide, amiloride, furosemide, spironolactone, bumetanide, ethacrynic acid, etc.
11.	Gastro-intestinal agents	- Cimetidine, ranitidine HCl, famotidine, domperidone, omeprazole, ondansetron HCl, granisetron HCl, etc
12.	Corticosteroids	- Betamethasone, beclomethasone, hydrocortisone, prednisone, prednisolone, methyl, prednisolone, etc.
13.	Antiprotozoal agents	- metronidazole, tinidazole, omidazole, benznidazole, clioquinol, decoquinate etc

Table 05: Marketed Rapid Dissolving Tablets in India

Name of the Product	Active Ingredients
Imodium Lingual	Imodium
Pepcidin Rapitab	Quick releasing antiulcer preparation of pepcid
Mosid – MT	Mouth melt tablet of Mosapride citrate.
Calritin Reditabs	Immediate Dissolving formulation of Calritin
Nimulid – MD	Nimesulide
Zyrof Meltab	Rofecoxib
Claritin Reditab	micronized loratadine
Feldene Melt	piroxicam (10 or 20 mg),
Maxalt-MLT	rizatriptan (5 or 10 mg), peppermint flavour
Pepcid RPD	famotidine (20 or 40 mg),
Zyprexa Zydis	olanzapine (5, 10, 15 or 20 mg),
Zofran ODT	ondansetron (4 or 8 mg), strawberry flavor
Remeron Soltab	mirtazepine (15, 30, or 45 mg), orange flavor

Packaging of FDT

Packing is one of the important aspects in manufacturing FDT. The products obtained by various technologies vary in some of the parameters especially in mechanical strength to a good extent. The products obtained by lyophilization process including various technologies such has Zydis, Lyoc, Quicksolv, and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture, and may degrade at higher humidity conditions. For the above reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Paksolv is a special packaging unit, which has a dome-shaped blister, which prevents vertical movement of tablet within the depression and protect tablets from breaking during storage and transport, which is used for Orasolv tablet. Some of the products obtained from Durasolv. WOW Tab, Pharmaburst oraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles.

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