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A Review On Rapimelt Tablets

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Abstract: Rapimelt Tablets are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Rapimelt tablets are also known as Mouth dissolving tablets, Orally disintegrating tablets, Melt - in - mouth, Fast dissolving drug delivery, Rapimelts tablets, Porous tablets, Quick dissolving tablets etc. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia, and Centre for Drug Evaluation and Research (CDER). Recently, ODT have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance especially in elderly and children. In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft - moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel - off blister packaging. Along with the rapid market growth of ODT products, the technologies, too, have advanced considerably over the years. The newest generation of ODTs can produce more robust, versatile tablets that overcome some of the limitations of earlier ODTs. Companies such as Eurand can produce pleasant tasting tablets, overcoming the common problem of poor drug taste compromising the benefits of an ODT.

Index Terms - Rapimelt Tablets, swallow, Mouth dissolving tablets, patient compliance, pleasant tasting tablets.

I. INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS has made a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly¹.

1.1 Advantages of Rapimelt Tablets²

- Improved compliance/added convenience
- Ease administration for patients who are mentally ill,
- No water needed
- Can be designed to leave minimal or no residue in mouth after administration and also to provide a pleasant mouth feel.
- No chewing needed.
- Better taste obtained by taste masking
- Improved stability, low sensitivity to environmental condition
- Suitable for controlled/sustained release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.

- Adaptable and amenable to existing processing and packaging high speed machinery.
- Cost- effective, lower production, packaging and distribution costs compared to current commercially available products.
- The technology is versatile and suitable for the development of enhanced products for veterinary medicines, OTC, Rx medicines & line extensions.
- The new proprietary method allows the incorporation of microencapsulated drugs for enhanced bioavailability, flexibility of dosing & immediate and/or controlled release.
- For superior therapeutic benefit.

1.2 Desired Criteria for Rapimelt Tablets³

- Not require water to swallow, but it should dissolve or disintegrate in the mouth within matter of seconds.
- Be compatible with taste masking
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Salient features of mouth fast dissolving tablets
- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feel property of MDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, and in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Pre gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

1.3 Ideal Characteristics of Rapimelt Tablets⁴

Mouth Feel:

Mouth-feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can an improved mouth-feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth-feel by reducing the "dryness" of a product.

Hygroscopicity:

Several fast dissolving 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.

Friability:

In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous or soft molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel off blister packing. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets, such as Wowtab by Yamanouchi- Shadlee and Dura Solve by CIMA labs.

1.4 FORMULATION OF ODT⁵

Excipients:

Excipients balance the properties of the actives in ODTs. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fastmelting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Bulking Materials:

Bulking materials are significant in the formulation of ODTs. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

Emulsifying Agents:

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

Lubricants:

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Flavours and Sweeteners:

Flavors and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavors can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition.

1.5 CHALLENGES IN FORMULATION OF ODTs⁶

1. Disintegration time and mechanical strength

ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile and there are chances that such fragile tablet will break during packing, transport or handling by the patients. Tablets based on technologies like Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential.

2. Taste masking

Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity. Number of techniques are developed for masking the bitter taste of most of the drugs, that includes formation of pellets by extrusion, spheronization or mass extrusion, coating of drug using a taste

masking polymer spray drying the drug dispersed in a polymeric solution, complexation of drug by inclusion in cyclodextrin drug-resinate complex formation microencapsulation of drug by polymer. Enhanced solubility of carvedilol by β -cyclodextrin as a complexing agent. Solubility studies were performed to investigate the drug carrier interaction. I.R. and D.S.C studies carried out to investigate any interaction and stability of formulation. Tablets were prepared by direct compression technique. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, drug content and in vitro drug release. It can be concluded that Carvedilol can be successfully complexed with Beta-cyclodextrin to prepare fast dissolving tablets in the ratio of 1: 4.

3. Sensitivity to environmental conditions:

ODTs generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in ODTs are meant to dissolve in minimum quantity of water.

4. Mouth feel

ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the ODTs should be as small as possible. ODTs should leave minimal or no residue in mouth after oral administration. Moreover addition of flavours and cooling agents like menthol improve the mouth feel.

5. Cost

The technology used for ODTs should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.

1.6 TECHNIQUES USED IN PREPARATION OF ODTs⁷

1. Freeze drying/ Lyophilization

Lyophilization means drying at low temperature under condition that involves the removal of water by sublimation. Drug in a water soluble matrix which is then freeze dried to give highly porous structure. The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermo-labile substances. Freeze drying process normally consists of three steps: Material is frozen to bring it below the eutectic point. primary drying to reduce the moisture around 4% w/w of dry product. Secondary drying to reduce the bound moisture up to required final volume.

2. Spray drying

This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets. 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. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

3. Molding

Tablets prepared by this method are solid dispersions. Molded tablets offer improved taste due to water soluble sugars present in dispersion matrix. Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum.

4. Sublimation

In this method a subliming material like (Ammonium bicarbonate, Ammonium carbonate, Urea, Benzoic acid, Naphthalene, camphor) is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores. where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

5. Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste.

6. Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to:

a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the super disintegrants.

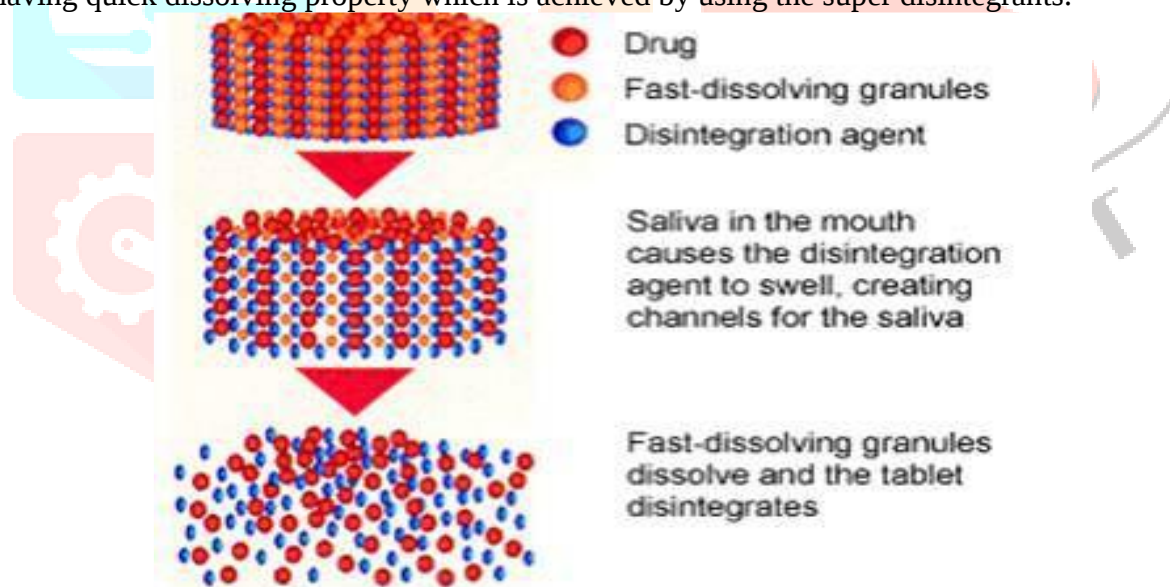


Fig. 1 Basic mechanism of Super disintegrants.

1.7 MECHANISMS OF SUPERDISINTEGRANTS⁸

There are four major mechanisms for tablet disintegration as Follows:

1) Swelling

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

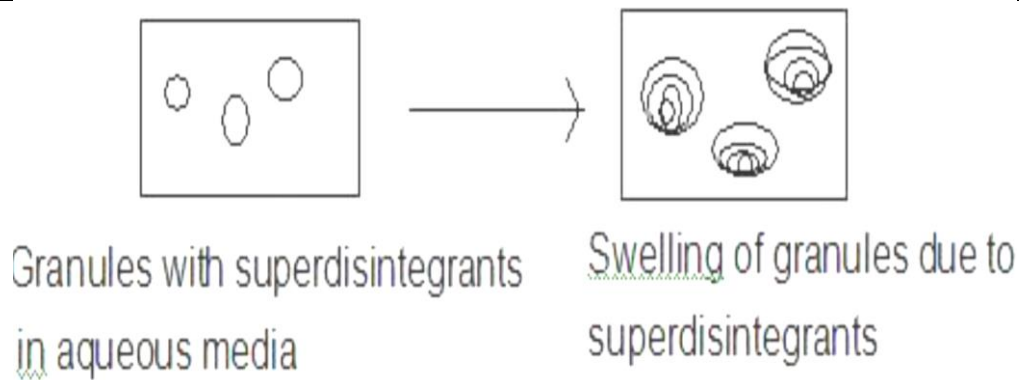


Fig. 2 Mechanism of superdisintegrants by swelling

2) Porosity and capillary action (wicking):

Tablet in the aq. Media leads to penetration of the medium into tablet and thus replacement of air adsorbed resulting in weakening of intermolecular bond and breaking of tablet into fine particles.

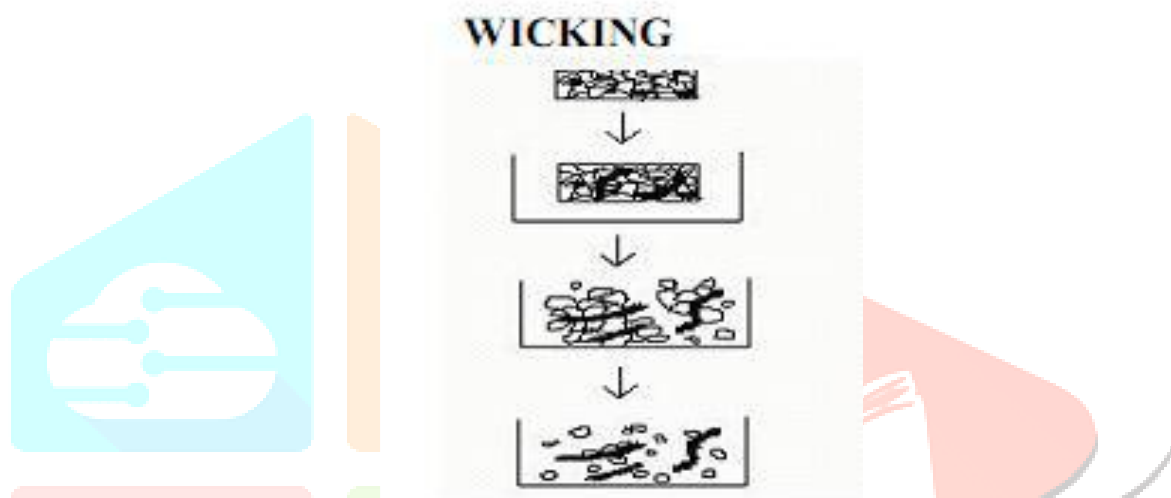


Fig. 3 Mechanism of superdisintegrants by Porosity and capillary action (wicking).

3) Due to particle-particle repulsive forces:

The electric repulsive forces b/w particles responsible for disintegration. It is secondary to wicking.

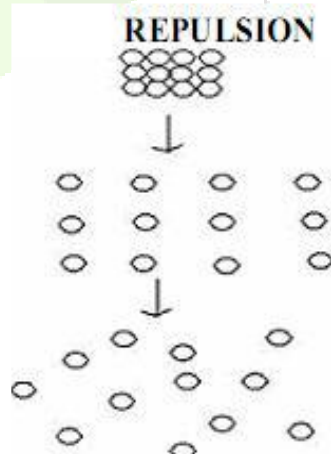


Fig. 4 Mechanism of superdisintegrants due to particleparticle

Repulsive forces

4) Due to deformation:

During tab. compression, disintegrated particles gets deformed and in contact with aq. media returns to normal structure (inc. in size). Eg: starch.

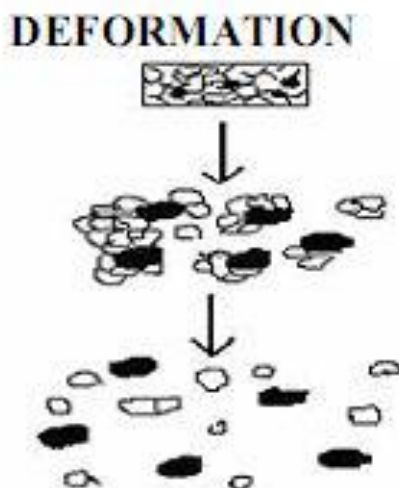


Fig. 5 Mechanism of superdisintegrant due to deformation

b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.

Advantages:-

It is cost effective due to low manufacturing cost, conventional equipments and limited number of processing steps.

Disadvantages:-

Differences in particle size and bulk density b/w the drug and diluents may lead to stratification within the granulation. Large dose may present problem if it is not easily compressible by itself. Avani RG et al³⁶ formulated Rapimelt tablet of ondansetron hydrochloride (HCl) by direct compression using sodium starch glycolate and croscarmellose as super disintegrant. These tablets were evaluated for weight variation, mechanical strength, *in-vitro* disintegration time, *in-vivo* disintegration time, and wetting time and drug release characteristics. Hardness and friability data indicated good mechanical strength of tablet. The results of *in-vitro* disintegration time and *in-vivo* disintegration time indicated that tablet dispersed rapidly in mouth within 3-5sec. It was confirmed that superdisintegrants addition technique is a useful method for preparing oro dispersible tablet by direct compression method. Sharma prepared fast-dissolving tablets (FDT) of promethazine theoclate by direct-compression method using Ac-Di-Sol, sodium starch glycolate and crospovidone in different concentrations. Different types of evaluation parameters for tablets were used. Tablets containing Ac-Di-Sol showed super organoleptic properties, along with excellent *in-vitro* and *in-vivo* dispersion time and drug release, as compared to other formulations. Prepared FDTs were evaluated for physico-chemical properties and *in-vitro* dissolution and concluded that the drug released from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing crospovidone.

7. Phase transition process

FDT were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95 °C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.

8. Cotton Candy Process

This process utilizes a unique spinning mechanism to produce floss-like crystalline structure. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to improve flow property and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to orally disintegrating tablet. This process can accommodate larger drug doses and offers improved mechanical strength. However, high-process temperature limits the use of this process.

9. Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poor water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

1.8 EVALUATION OF ODTs⁹

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

Hardness/crushing strength

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for an ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The crushing strength of the tablet may be measured using conventional hardness testers.

Friability

To achieve % friability within limits for an ODT is a challenge to the formulator since all methods of manufacturing of ODT 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 ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies The wetting time of the tablets can be measured using a simple procedure 50 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 equation: $R = 100 (W a - W b) / W b$.

Moisture uptake studies

Moisture uptake studies for ODT 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 ODTs 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 ODT should mimic disintegration in mouth with in salivary contents.

Dissolution test

The development of dissolution methods for ODTs 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 ODT. Other media such as 0.1 N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for ODT 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. USP 2 Paddle apparatus, which is the most suitable and common choice for ODTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of ODT is very fast 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.

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