Review Article

Technologies, Evaluation and Development of Oro- Dispersible Tablet: A Review

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ABSTRACT

Advances in Novel Drug Delivery Systems (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve patient compliance. One such approach is oro-dispersible tablet/mouth dissolving tablet formulation. The demand for Oro-dispersible tablet (ODT) has been growing during the last decade especially for elderly patients and children who have swallowing difficulties. Various techniques employed to prepare ODTs, evaluation methods and a patented technology along with recent research in this area is reviewed in this article. Their increasing importance was underlined recently when European Pharmacopoeia adopted the term Orodispersible Tablet as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. The acceptance of rapidly disintegrating oral tablet dosage forms are increasingly being recognized in both, industry and academia.

Keywords: Orodispersible tablet, patented technology, Formulation techniques.

INTRODUCTION

Many patients find difficulty in swallowing tablets and hard gelatin capsules and hence do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy[1].

Recent advances in Novel Drug Delivery System (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance[1].

Nearly 35% of the general population, especially the elderly patients and children suffer from dysphagia or difficulty in swallowing. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally illness, developmentally disabled, non-cooperative patients and patients with reduced liquid intake plans or patients suffering from nausea. The swallowing problems are also common in some cases such as[2] patients with motion sickness, sudden episodes of allergic attack or coughing and due to lack of water. To overcome these problems, formulators have considerably dedicated their effort to develop a novel type of tablet dosage form for oral administration i.e., one, which disintegrates and dissolves quickly in saliva without the need for drinking water. This tablet disintegrates instantaneously or disperses in the saliva[3]. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva passes down into the stomach and produce rapid onset of action. In such circumstances, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[4]. The advantages of rapidly disintegrating tablets are increasingly being recognized in both, industry and academia. Their increasing importance was underlined recently when European Pharmacopoeia[5] adopted the term *Orodispersible Tablet* as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.

Desired Criteria for Orodispersable Drug Delivery System

1. Compatible with taste masking.
2. Have a pleasant mouth feel.
3. Leave minimal or no residue in the mouth after oral administration.
4. As such it does not require water to swallow, but it should dissolve or disintegrate in the mouth within seconds.

Salient Features of Oro Dispersable Tablets

1. Ease of administration to patients who refuses to swallow tablets and capsules, such as pediatric, geriatric and psychiatric patients.
2. Rapid dissolution and absorption of drug, which will produce quick onset of action.
3. Convenience and patient compliance for disabled, bed-ridden patients and which is highly convenient to patients who are traveling and do not have immediate access to water.
4. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
5. Pregastric absorption can result in improved bioavailability and as a result of reduced dosage;

improve clinical performance through a reduction of unwanted effects.

6. Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
7. Leave minimal or no residue in the mouth after oral administration.
8. Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
9. Exhibit low sensitivity to environmental conditions such as humidity and temperature.

A wide range of drugs such as cardiovascular drugs, analgesics, antihistamines, anti emetic's, anti-convulsants, anti-parkinson's, anti-psychotic, anti-spasmodic, neuroleptic and drugs for erectile dysfunction can be considered as candidates for this dosage form. Hence there has been an enhanced demand for more patient compliance dosage forms[6].

The importance of rapidly disintegrating oral tablet dosage forms are increasingly being recognized in both, industry and academia[7]. Their increasing importance was underlined recently when European pharmacopoeia adopted the term – Orodispersible Tablet as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.

Ideal Characteristics of Orodispersible Tablets [8]:

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 improve 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.

FORMULATION OF ODTs

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 fast melting 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.

Flavors 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.

Techniques for ODTS

Various processes employed in formulating ODTs include freeze-drying, cotton candy process, molding, spray drying, mass extrusion, and compaction.

Tablet Molding

In this method, the delivery system is prepared in the form of tablets using water soluble additives to allow the tablet to dissolve rapidly and completely in mouth[7,9]. All the ingredients of the formulation are passed through fine mesh, dry blended, wetted with a hydro-alcoholic solvent and then compressed into tablets using low compression forces. The solvent is then removed by air drying[10].

Freeze Drying (Lyophilization)

Lyophilization is a pharmaceutical manufacturing technology, which allows drying of heat-sensitive drugs and biological at low temperatures under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

Spray Drying

Spray drying is a process by which highly porous, fine powders can be produced. The composition contains a bulking agent (mannitol and lactose), a disintegrant (sodium starch glycolate and croscarmellose sodium), an acidic ingredient (citric acid) and/ or alkaline ingredients (sodium bicarbonate) which when compressed into tablets shows fast disintegration and enhanced dissolution.

Sublimation

This method includes the addition of a sublime salt to the tableting components, compressing the blend and removing the salt by the process of sublimation. The active ingredient, a diluent, a sublime salt (camphor/ ammonium bicarbonate), a binder and other excipients are blended and tablets are prepared[11].

Addition of Disintegrants

Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. Microcrystalline cellulose, cross-linked carboxy methyl cellulose sodium, cross-linked polyvinyl pyrrolidone and partially substituted hydroxy propyl cellulose, absorbs water and swell due to capillary action and are considered as effective disintegrants in the preparation of fast dissolving tablets.

Sugar Based Excipient

Sorbitol, mannitol, dextrose, xylitol, fructose, maltose and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar-based materials.

Mass Extrusion

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 upon heated blade to form tablets.

Patented Technologies

Patented technologies for ODT's are summarized as below

Zydis

This technology converts the mixture of active ingredient and water dispersible carrier materials into open matrix network that disintegrates rapidly[12] using freeze drying process. The network is highly porous solid foam, which allows rapid penetration of liquid and facilitates quick disintegration of the dosage unit. In Zydis technology, drug is added to a solution of carrier material (preferably gelatin) to obtain dispersion, and the dispersion is filled into preformed pockets of blister pack by automatic means and freeze dried to produce the final dosage form.

Eg.-Olanzapine (ZyprexaZydis)[13, 14].

OraSolv

This system essentially makes tablets that contain the taste masked active ingredients and an effervescent disintegrating agent, which on contact with saliva, rapidly disintegrates and released the active ingredient. The tablets are made by direct compression at very low compression forces in order to minimize oral dissolution time. The tablets produced are soft and friable.

Eg. - Paracetamol (Tempra Quicklets)[15, 16].

Dura Solv

The tablet made by this technology consists of a drug, fillers and a lubricant. DuraSolv tablets are prepared by using conventional tableting equipment and have good rigidity. It is an appropriate technology for products requiring low amounts of active ingredients.

eg-Zolmitriptan (Zolmig ZMT)[17].

Flash Dose

Flash dose tablets consist of self-binding shear form matrix termed as —floss. Shear form matrices are

prepared by flash heat processing and are of two types. Ten (10) Single floss or unifloss, consisting of a carrier and two or more sugar, alcohols, of which one is xylitol.

Dual floss consists of a first shear form carrier material (termed – base floss contains a carrier and at least one sugar alcohol generally sorbitol) and a second shear form binder matrix (– binder floss, contains a carrier and xylitol).

In flash heat process, the feedstock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibers. The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. The so formed matrices are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug. The shear form matrix is blended with drug and other tableting ingredients and compressed into tablets using conventional tableting equipment. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

Eg.-Tramadol Hcl (Relivia Flash dose)[18, 19].

Wow Tab

This process uses a combination of low mouldability saccharide (rapid dissolution) and high mouldability saccharide (good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (lactose, mannitol) and granulated with a high mouldability saccharide (maltose, sorbitol) and compressed into tablets[20].

Eg.-Famotidine (Gaster D)[21, 22].

Flash Tab

This technology involves the preparation of rapidly disintegrating tablet, which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, extrusion-spheronization or simple pan coating method. The microcrystals or microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets.

Eg.-Ibuprofen (NurofenFlash Tab)[23].

Evaluation of ODTS

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.

The wetting time of the tablets can be measured using a simple procedure[24] 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.

Kancke 51 proposed 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.

Fineness of Dispersion[25]

This is a qualitative test specified by EP for dispersible tablets[26]. This test is recommended for performing on tablets which are not truly mouth dissolving, but are fast oral disintegrating tablets (ODT's). 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.

Recent Research on ODTS

Several studies reported the formulation and evaluation of ODT's of various drugs for different purposes. Recent research on ODT's is summarized in following Table.

Sr. No	Drug (therap. category)	Method used	Excipients used	Result	Reference
1	Nateglinide (anti hyperglycemic agent)	Direct compression	Pregelatinized starch, sodium starch glycolate, crospovidone.	Better patient compliance,	27
2	Celecoxib (NSAID)	Direct compression	Microcrystalline cellulose, crospovidone, AC-DI-sol,	Increased bioavailability.	28
3	Rosuvastatin (HMG-CoA reductase)	Solid dispersions	Croscarmellose sodium, sodium Starch glycolate, Pregelatinized starch, mannitol, PEG 6000.	Enhance solubility, dissolution rate.	29
4	Carbamazepine (tricyclic anti-depressants)	Solid dispersions	Croscarmellose Sodium, PVP, Aspartame, Microcrystalline cellulose, PEG6000, sodium laurylsulphate.	Improved bioavailability, better patient compliance.	30
5	Montelukast Sodium (Antineoplastic)	Direct compression	Crospovidone, Sodium starch glycolate, Mannitol Microcrystalline cellulose	Enhanced dissolution rate	31
6	Salbutamol Sulphate(β2 receptor agonist)	Direct compression	Primogel, L-hydroxy Propyl cellulose, Microcrystalline cellulose, Mannitol-D	Rapid dissolution and rapid onset of action	32

7	Metformin hydrochloride(oral antidiabetic biguinide agent,)	Direct compression	crosspovidone, sodium starch glycolate, Mannitol, microcrystalline cellulose, Croscarmellose sodium	98.37% of drug is released within 30 minutes.	33
8	Oxcarbazepine (NSAID)	Wet granulation	Avicel pH 102, Aerosil	Enhanced dissolution.	34
9	Clonazepam (Antiepileptic)	Direct compression	Crospovidone, Croscarmellose, Directly Compressible Mannitol,	Enhanced patient compliance	35
10	Rizatriptan benzoate (Serotonin 5-HT receptor agonist)	Mass extrusion	Eudragit EPO, Sodium starch glycolate, Croscarmellose sodium, Crospovidone, Pearlitol SD200	Complete taste masking, rapid disintegration and dissolution	36

CONCLUSION

ODT's can be prepared for different drug by various technology for different drugs and the prepared tablets are with good drug release, which is evaluated by various parameters such as hardness, fariability, dissolution rate and disintegration time of the prepared tablet.

ODT's will help the patient to overcome the difficulty in swallowing (Geriatric & Pediatric). Other swallowing issues related to motion sickness, sudden episodes of allergic attack or lack of water as ODT's don't require water, as they come in contact with saliva they disintegrate rapidly within seconds. Hence this rapid dissolution and absorption will produce quick onset of action of drug.

Orodispersible tablets (ODT's) are innovative drug delivery systems and have potential advantages over conventional dosage forms. Though considerable research has been done in the formulation development and technologies for ODT's, more intensive investigations are to be carried out in this promising area to result in newer cost effective technologies and better products.

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