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Review Article

ORALLY DISINTEGRATING TABLETS: AN OVERVIEW

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Abstract: Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Recent advances in technology prompted researchers and scientists to develop oral disintegrating tablets (ODTs) with improved patient convenience and compliance. ODTs are solid unit dosage form which dissolve or disintegrate rapidly in the mouth without water or chewing. Novel ODT technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatric, geriatric and psychiatric patients who have difficulty in swallowing (Dysphagia) conventional tablet and capsules. Technologies used for manufacturing of ODTs are either conventional technologies or patented technologies. This review depicts the various aspects of ODT formulation, superdisintegrants and technologies developed for ODT, along with various drugs explored, evaluation tests and marketed formulations in this field.

Key words: Orally disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, chewing gums, fast dissolving films, superdisintegrants

INTRODUCTION

A vast variety of pharmaceutical research is directed at developing new dosage forms. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists. Table **1** enlists the various drugs and ingredients formulated in to orally disintegrating tablets (ODT).

The concept of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication.

Interestingly, the demand for ODT has enormously increased during the last decade, particularly for geriatric and pediatric patients who experience difficulty in swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high incidence of ineffective therapy.

In disease conditions such as motion sickness, sudden episodes of attacks of coughing and repeated emesis swallowing conventional tablets become difficult. Orally disintegrating dosage forms can serve as an effective alternative mode of drug delivery in such situations. When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva. Thereafter, the drug may get absorbed from the pharynx and oesophagus or from other sections of G.I.T as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form [1-5]. Hence, orally disintegrating systems may be anticipated to result in achievement of the required peak plasma concentration rapidly for drugs stable in the gastric pH. The orally disintegrating dosage forms could be suitable for neuroleptics, cardiovascular agents, analgesics, anti-allergics and drugs for erectile dysfunction. In the light of the above, the present article aims at critically analyzing various formulation and technological developments with respect to orally disintegrating systems.

ORALLY DISINTEGRATING TABLETS

The centre for drug evaluation and Research defines orally disintegrating tablets as a dosage form –"A solid dosage form which disintegrates rapidly within a matter of seconds when placed under the tongue". The disintegrating time for orally disintegrating tablet varies from seconds to minutes, depends upon the size of tablet and formulation. European pharmacopeia defined orally disintegrating tablets as-"Uncovered tablet which disperse before ingestion in the buccal cavity". Different technological techniques such as freeze drying or moulding or direct compression etc.are used to prepare the formulation of this type in the pharmaceutical market[7].

Advantages of ODT:

1. It can be administered to the patient who cannot swallow conventional dosage form such as bedridden patients, elderly and patient effected by renal failure and thus improves patient compliance[11].
2. It is suitable for bedridden, disabled, traveller and busy persons who does not contain water every time[10].
3. Good mouth feel property helps to mask the bitterness of medicines.
4. Rapid drug therapy intervention.
5. It provides rapid absorption of drugs and increased bioavailability.
6. No chewing needed[13].

Disadvantages of ODT's:

1. It requires proper packaging for safety and stabilization of stable drugs.
2. It is hygroscopic in nature, so must kept in dry place[9, 13].
3. It shows the fragile, effervescence granules property[6].
4. If not formulated properly, it may leave unpleasant taste in mouth.
5. Since the tablet having insufficient mechanical strength, so careful handling is required[8].

Traditional taste masking technologies in ODTs[27]:

1. Taste masking by Ion-exchange Resins.
2. Taste masking by coating with Hydrophilic Vehicles.
3. Taste masking using Flavors and Sweeteners.
4. Taste masking using Lipophillic Vehicles

Table: 1- Technologies Used For Masking the Taste of Active Ingredient [27, 28, 30]:

S. No.	Technology	Excipients	Active Ingredient	Method
1	Fluidized bed coating	Methyl cellulose (MC), Acesulfame(AS), HPMC	Northindrone, tamoxifen, caffeine, acetaminophen, rilmazafone HCl	MC and AS solution charged to fluidized bed drier containing sieved northindrone. - Internal temperature maintained at 115˚F - Coating completed in 3 min.
2.	Agglomeration process	Sweetener :- Sodium saccharin; acesulfeme Dry blend;- HPMC Silica dioxide Polythiazide	Polythiazide	Sweetener solution sprayed on dry blend to form agglomerated granules - Wet mixture was dried in a convection oven at 103˚F for 17 hrs. - Dried product size reduced, sieved (#100)
3	Pelletization process	Dry Blend:- Aspartame, HPC and Gum arabic	Loratidine	Crushed ice was mixed with dry blend mixture to form spherical particles. - Wet spherical particles were dried in a tray drier at 55˚C
4	Infusion method	Dry blend:- Sucralose, Fluoxetine and Polyvinyl pyrrolidone	Fluoxetine	Propylene glycol: water (40:60) was used to mix dry blend, HPMC was added. Mixing was continued at high speed for 3 min. The particles obtained were screened (#100)

Formulation aspects in developing ODT:

ODT's are formulated by several processes, which differ in their methodologies and vary in various properties such as:

1. Taste and mouth feel [7].
2. Mechanical strength of tablets.
3. Drug dissolution in saliva.
4. Bioavaibility.
5. Swalloability [11]

Challenges in formulating orally disintegrating tablets:

1. **Mechanical strength:**

In order to swallow ODTs to disintegrate in the oral cavity, they are either made of porous or soft molded matrices, which makes tablet friable and difficult to handle and hence requires peel-off blister packing which increases its cost. [22, 23]

2. **Palatability:**
   Since most drugs are unpalatable, orally disintegrating drug delivery system contains medicament in taste masked form.[24] It dissolves in patient oral cavity, thus release the active ingredient which comes in contact with the taste buds [10].
3. **Aqueous solubility:**
   Water soluble drugs pose various formulation challenges results in freezing point depression and formation of glassy solids that may collapse upon drying. Such collapse can be prevented by using various matrix forming excipients like mannitol. [11, 15]
4. **Amount of drug:**
   The application for technologies used for ODTs is limited by the amount of drug into each unit dose. The drug dose must be lower than 400mg for insoluble drugs and 60mg for soluble drugs. [23]
5. **Size of tablet:**
   The easiest size of tablet to swallow is 7-8mm while the easiest size to handle is 8mm.Therefore, tablet size that is easy to handle and easy to take is difficult to achieve.
6. **Hygroscopicity:**
   Many orally disintegrating dosage forms are hygroscopic in nature. [6, 7, 10] Hence they need protection from humidity.

Mechanism of ODTs : [26]

It involves the following mechanism –

1. Incorporation of an appropriate disintegrating agent in the tablet formulation.
2. For rapid disintegration and dissolution of the tablet, water must quickly enter into tablet matrix.
3. Tablet is broken down into smaller particles.

Excipients used for preparation of ODTs : [10, 26, 27, 14]

1. **Superdisintegrants**- It increases the rate of disintegration and dissolution. For the success of orally disintegrating tablet, the tablet having quick dissolving property which is achieved by super disintegrants.Examples are-Crospovidone, MCC, Sodium starch glycolate, CMC, Carboxy methyl cellulose and modified corn starch.
2. **Sweeteners and sugar based excipients**-Sugar based excipient act as bulking agents. They exhibit high aqueous solubility and sweetness and impart taste masking property. Examples are-Aspartame, Sugar derivative, Dextrose, Fructose, Mannitol, Sorbitol, Maltose etc.
3. **Flavors**-It increases patient compliance and acceptability. Examples are-Vanilla, Citrus oil, Fruit essence, Eucalyptus oil, Clove oil, Peppermint oil etc.
4. **Surface Active agents**-It reduces interfacial tension and thus enhances solubilization of ODTs.Examples are-Sodiumlaurlysulfate, Sodiumdoecylsulfate, Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene steartes etc.
5. **Binder**-It maintains integrity of dosage form. Examples are-PVP, Polyvinylalchol, Hydroxy propyl methylcellulose.
6. **Colour**-It enhances appearance and organoleptic properties of dosage form. Examples are-Sunset yellow, Red iron oxide, Amaranth. [8]
7. **Lubricants**-It helps reduces friction and wear by introducing a lubricating film. Examples are-Stearic acid, Magnesium stearte, Zinc stearte, Talc, Polyethylene glycol, Liquid paraffin, Colloidal silicon-di-oxide etc.
8. **Fillers**-It enhances bulk of dosage form. Examples are-Mannitol, Sorbitol, Xylitol, Calcium carbonate, Magnesium carbonate, Calcium sulfate, Magnesium trisilicate etc.

Techniques used for preparation of ODT's:

A. Conventional techniques: Various co conventional techniques are available for preparation of ODT's are-

1. **Freeze drying:** It is a process in which water is sublimated from the product after freezing. In this heat sensitive drugs and biological are dried at low temperature that allows removal of water by sublimation. [31]
2. **Sublimation:** In these, inert solid ingredient that volatilized readily was added to other tablet ingredient and mixture is compressed into tablets. The volatile material was then removed by the process of sublimation.[29, 36]
3. **Spray-drying**: It produces very fine and highly porous powder. Tablets prepared

from spray drying disintegrate within 20 sec when immersed in an aqueous medium[27].

4. **Molding**: In these, water soluble ingredients are used to prepare molded tablets so that tablet dissolves rapidly. Molded tablets are very less compact then compressed tablets and exhibit porous structure for rapid dissolution.
5. **Mass-extrusion**: It involves softening the active blends using the solvent mixture of water soluble PEG. The granules of bitter tasting drugs are coat by dried cylinders and hence masking their bitter taste. [32, 34]
6. **Disintegrates addition**: Because of its easy implementation and cost effectiveness, it is a popular technique for formulating ODT's. The basic principle involved is addition of superdisintegrants in optimum conc.
7. **Direct compression**: It is the easiest way of manufacturing tablets. It consists of a limiting number of processing steps, conventional equipments and commonly available excipients. Also it requires few unit operations as compared to wet granulation.[7, 20]

Table:2-Ingredients and Technologies Used for Formulating Orally Disintegrating Systems:

Orally Disintegrating System	Drug	Disintegrating Agents	Other formulation Ingredients	Technology	Disintegration Time	Ref.
FDT	Capecitabine	Crospovidone (intragranular and extragranular)	Hypromellose (binder), mannitol, microcrystalline cellulose, Pharmaburst C	Wet granulation and compression	50 sec (for 125mg tablet)	[15]
FDT	Acetaminophen and / or Sodium ibuprofen, Ibuprofenlysine, Naproxen Sodium, Flurbiprofen Sodium, Diclofenac Potassium	Xylitol, croscarmellose sodium, acetaminophen and NSAID for preparing melt mass granules	Microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, stearic acid	Melt extrusion method and compression	Less than 60 sec	[16]
FDT	Amlodipine Besilate	Avicel PH 101 or 301, mannitol	Eudragit EPO	Direct compression followed by sublimation	0.25-.63 min	[17]
FDT	Modafinil	Croscarmellose sodium, MCC	Lactose, pregelatinized starch	Wet granulation	---	[18]
FDT	Resperidone	Mannitol, aspartame, PEG 400, PEG 4000.	MCC (Ph 200), Gelucire 44/14	Spray drying and compression	Less than 30 sec	[19]
FDT	Clarithromycin or Cefixime	Carrageenan NF, tricalcium phosphate,	Pellets of drug composed of Avicel PH 105, Low-substituted hydroxypropylcellulose , Sucrose stearate	Extrusion-spheronization	Less than 60 sec	[20]
FDT	Famotidine	Mannitol, PVP K30, dextran, sucralose	Sugar spheres, lactose	Freeze drying	2-6 sec	[21]

B] Patented technologies: Various patented technologies available for preparation of ODT's are-

1. **Flashtab Technology**: In these, tablets consists active ingredient in the form of micro crystals. It is conventional tableting technology. Prographarm laboratories have patented the flashtab technology. [29]
2. **Wow tab Technology**: It involves adequate dissolution rate and hardness .It is patented by "Yamanouchi Pharmaceuticals Co". Wow means without water.
3. **Flash dose Technology**: It requires greater surface area for dissolution. Flash dose tablets consist of self binding shear form matrix termed as "floss". It has been patented by "Fuisz".
4. **Durasolv Technology**: It is a patented technology of "CIMA" labs. It consists of

druf, fillers and lubricant. It requires low amount of active ingredient [23]

5. **Zydis Technology**: It involves quick dissolution, increased bioavailability and self-preserving. It involves softening the active blends using the mixture of methanol and polyethylene glycol.
6. **Orasolv Technology**: It is patented technology of "CIMA" labs. It involves quick dissolution and taste masking of active ingredient. [29, 37]

Evaluation parameters:

Precompression parameters: [37, 38, 39, 40]

1. **Bulk Density (D_b):** It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$D_b = M / V_b,$$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

2. **Tapped Density (D_t):**It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$D_t = M / V_t$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

3. **Angle of Repose (Θ):** The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan(\Theta) = h / r$$

$$\Theta = \tan^{-1} (h / r)$$

Where, Θ is the angle of repose. ,

h is the height in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table :3- Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose(^{0})	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	**>34**	**Very Poor**

4. **Carr's index (or) % compressibility:** It indicates powder flow properties. It is expressed in percentage and is give by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, Dt is the tapped density of the powder and

Db is the bulk density of the powder.

Table:4- Relationship between % compressibility and flow ability

Sr no.	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very Poor
6	<40	Very Very Poor

4. **Hausner ratio:** Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters:

1. **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 No. 5

Table -5: Weight Variation Specification as per IP

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

2. **Hardness:** Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

3. **Thickness:** Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper. [42]

4. **Friability (F):** Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula. [43]

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

5. **Wetting time:** Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders(R).

$$dl/dt = r¡cos\Theta/(4hl)$$

Where,
l is the length of penetration,
r is the capillary radius,
¡ is the surface tension,
h is the liquid viscosity,
t is the time, and
Θ is the contact angle.

It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^oC.Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

6. **In-Vitro drug release:** Release of the drug *in vitro*, was determined by estimating the dissolution profile.

7. **In vitro dissolution studies:** ODTs were evaluated for dissolution behaviour. Dissolution tests used the USP apparatus 2, paddle types (Elect lab, Mumbai, India.). Dissolution was carried out with the rotation speed of 50 rpm using 500 ml of 0.1 N HCl as the dissolution medium maintained at a temperature of 37 ± 0.5oC19.
8. **Assay:** 10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in pH 1.2 buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH 1.2. Absorbance was read at 210 nm against the reagent blank, and the concentrations of Azithromycin in µg/ ml was determined by using the regression equation –

Y = 0.007x + 0.001

Drug content in mg / tablet = conc. µg/ml * dilution factor

% Drug content = drug content in mg * 100 / label claim.

FUTURE DEVELOPMENTS

Mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. In addition, MDTs may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Because drugs delivered in MDTs may be absorbed in the pre-gastric sites of highly permeable buccal and mucosal tissues of the oral cavity, they may be suitable for delivering relatively low-molecular weight and highly permeable drugs.

Future possibilities for improvements in MDTs and drug delivery are bright, but the technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from MDTs have yet to be fully realized.

STABILITY STUDIES

The purpose of the stability testing is to provide evidence on the quality of a drug substance or its product, which varies with time under the influence of environmental factors such as temperature, humidity and light. Recommended storage conditions, re-test periods and shelf lives are to be established.

The International Conference on Harmonization (ICH) Guidelines titled “stability testing of New Drug substances and products” (QIA) describes the stability test requirement for drug registration applications in the European Union, Japan and United States of America.

Protocol for stability studies:

1. **Storage condition:**

Ambient condition: 25 ºC ± 2 ºC / 60% RH ± 5%

Accelerated condition: 40 ºC ± 2 ºC / 75% RH ± 5%

2. **Packing:** The selected formulations were packed in amber- colored bottles, which were tightly plugged with cotton and capped with aluminium.
3. **Testing intervals:** Stability studies were carried out at 25 ºC / 60% RH & 40 ºC / 75% RH for the selected formulations at intervals of initial, 30 days, 60 days and 90 days.
4. **Testing parameters:** The stored samples were evaluated for Weight variation, Hardness, Disintegration Time, Friability, Wetting Time and Drug content at the interval of 1 month.

CONCLUSION

The area of formulating orally disintegrating dosage forms is aims at increasing the patient compliance and decreasing the disintegration time. It also aims of masking the objectionable taste of active ingredients. As compared to other complicated processes such as freeze drying etc., formulation of orally disintegrating dosage form is easy and overall cost of manufacturing is low. The potential of orally disintegrating dosage form to disintegrate in the oral cavity within seconds, fast onset of action, increasing patient compliance and taste masking of active ingredient makes it an attractive drug delivery form. However, an addition of active ingredient in dosage form like orally disintegrating tablets, orally disintegrating films, oral wafers, buccal patches and chewing gums are excepted to provide a highly acceptable means of delivering drug to geriatric and paediatric patients. So in forth coming years oral drug delivery becomes a much popular drug delivery.

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