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Review Article

An Updated Review on Orodispersible Table (ODTs)

Saini Pushpendra Kumar*, Arora Namita

Department of Pharmaceutica Science, Lords University, Alwar, Rajasthan.

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ABSTRACT

In recent times, there has been an enhanced demand for more patient compliant dosage forms. Oral route has been the gold standard in the administration of medications due to its safety, good patient compliance, ease of ingestion, pain avoidance and. The pediatric and geriatric populations may benefit from advantages such as simplicity of administration and convenience of usage. Mentally retarded patients, institutionalized patients and those travelling without access to water face a challenge as well. ODTs are solid unit dosage form which when placed in the oral cavity swiftly disintegrates or dissolves without the need of water. ODT technology helps overcome the above mentioned challenges. Several orodispersible medication formulations have recently been brought to the market. The use of oral lyophilizers and orodispersible granules or films has expanded the therapeutic options. This study focuses on ODTs, a novel method in drug delivery systems increasingly emphasized in the formulation industry. Due to super disintegrants in the formulation, an orally disintegrating tablet dissolves in the mouth within a minute in the presence of saliva and without the need to drink extra water. This study focused on the technologies that are now accessible and the progress that has been achieved in the field of ODTs manufacturing. Apart from traditional formulation processes, this review delves into the details of certain novel technologies such as freeze drying, direct compression, tablet molding, sublimation, and fast dissolving films, as well as their benefits and drawbacks. Several scientists have created ODTs using patented technologies such as Zydis, wow tab, flash tab, Oroquick, and Orosolv technology.

Keywords: Bioavailability, Superdisintegrants, Patented technologies, Direct compression, ODTs.

INTRODUCTION

The oral route of medicine administration is the most common and recommended way of drug delivery for both solid and liquid dosage forms. Orodispersible tablets (ODTs) are solid single-unit dosage forms put in the mouth, allowed to disperse/dissolve in saliva, and then taken without water versatility (Bandari, Mittapalli, & Gannu, 2008)[1]. Difficulty swallowing (dysphasia) is frequent in all age groups, particularly the elderly, and can also be noticed while taking traditional pills and capsules. This condition is linked to various severe disorders, including stroke, Parkinson's disease, AIDS, and other neurological diseases such as cerebral palsy. ODT is simple to administer because no water is necessary for ingesting the pills, making it appropriate for elderly, pediatric, and travelling patients (Ghosh, Ghosh, & Prasad, 2011)[2]. ODTs have tremendous advancement in drug delivery, the oral route is the ideal and preferable route for the administration of therapeutic agents because of low-cost therapy, it tends to the high level of patient compliance (Arora & Sethi, 2013)[3]. This article contains inventive technologies, the dosage form containing active pharmaceutical ingredients (API). ODTs have been researched for their potential to increase the bioavailability of poorly water-soluble drugs by modifying the drug's dissolving profile, in addition to improving patient compliance. Nonetheless, because of ODT's rapid Disintegration, the active substance comes into contact with taste receptors, and the need for a pleasing flavor becomes a critical part of patient palatability. As a result, masking the taste of unpleasant active chemicals is a significant barrier to overcome to manufacture ODT products properly. In summary, oral administration of bitter active compounds via ODT formulations should result in greater patient compliance, improved palatability, and a favorable therapeutic outcome.

ODTs when placed in the oral cavity swiftly melt in saliva without the need of water and disperse rapidly before swallowing. In cases like this, Bioavailability is significantly more than that seen from typical tablet type of dosage. The Unites States Food and Drug Administration (USFDA) have defined ODT as "A solid dosage form containing medicinal substance or therapeutic agent which disintegrates usually within a matter of seconds when placed upon the tongue"(Martínez-Terán, Hoang-Thi, & Flament, 2017)[4]. Generally, the disintegration time for ODT varies from few seconds to around a minute. ODT's are also known as mouth dissolving tablets, melt-in mouth tablets, fast dissolving tablets, rapid melts, porous tablets and quick dissolving tablets. Commercially marketed ODT is manufactured using various methods, such as lyophilization, molding, freeze drying, sublimation, rapid dissolving films, and direct compression. The lyophilization and molding methods generate ODT that disintegrates in approximately 30 seconds despite having minimal physical resistance and great friability. On the other hand, tablets produced by

**Author for Correspondence :* sainipushpendrakumar@gmail.com

direct compression are less brittle but disintegrate more slowly (Bangale, Shinde, & Rathinaraj, 2011)[5].

Ideal Properties of ODTs (YAPAR, 2014)[6]

1. Does not require water or substitute liquid to swallow.
2. Rapidly dissolves and disintegrates in saliva within a matter of seconds.
3. Have a pleasant taste and mouth feel.
4. Easily transportable and mobile.
5. Leave no/negligible residue in the mouth after administration.
6. Be able to manufacture in a simple conventional way with low cost.
7. Withstand environmental conditions like humidity, temperature etc.

Salient features of ODTs (Hirani, Rathod, & Vadalia, 2009)[7]:

- Easily ingested by the patients who don't swallow such as pediatric, gediatric, patients who are psychiatric, bedridden patients and patients affected by renal failure.
- It produces quick onset of action due to rapid disintegration, dissolution and absorption of tablets.
- The good mouth feel property of the drug helps to change the perception of medication as "bitter pill" particularly in pediatric patient.
- The pregastric absorption results in improved bioavailability and less dosage improves clinical performance by reducing the side effects.
- Due to solid form of drug it is stable for long duration of time.

Advantage of ODTs (Garud, Derle, Valavi, Shaikh, & Derle, 2014)[8]:

- Improved stability
- Suitable for controlled/sustained Offers improved compliance and convenience to patients and prescribers.
- It improves patient adherence and reduces the development of resistance in the case of antimicrobials.
- Simplifies the logistics of procurement and distribution
- For Rapid drug delivery, ODTs are considered to be preferred dosage form
- The drug is released quickly from this dosage form and gets dissolve in GIT tract without getting into the stomach, increased bioavailability can be achieved
- ODTs are very convenient for administering to various classes of patients from disabled, travelers and busy people, who do not always have access to water
- Some drugs are absorbed from the pharynx and esophagus as the saliva passes down into the stomach; in such cases, the bioavailability of drugs is increased
- No water needed
- No chewing needs, better taste, release actives, Allow high drug loading

Disadvantage of ODTs (Garud et al., 2014)[9]

- Rapid drug therapy intervention is not possible
- Sometimes may require more frequency of administration
- Dose dumping may occur
- Reduced potential for accurate dose adjustment
- For properly stabilization and safety of the stable product, ODT requires special packaging
- Usually have insufficient mechanical strength. Hence, careful handling is required
- Leave unpleasant taste and/or grittiness in the mouth if not formatted properly.

Super disintegrants

Disintegrating agents overpower the cohesive strength provided during compression, thereby helping to dissolve the tablet and increasing the surface area for dissolution. Several newer agents have been synthesized that are more efficient at lower concentrations with greater mechanical strength and disintegrating efficiency. These agents are called 'Superdisintegrants'. Superdisintegrants play a major role in achieving the desired rapid melt / oral disintegration of tablets (Mohanachandran, Sindhumol, & Kiran, 2011)[10].

Ideal properties of Super disintegrants

- Poor solubility.
- Poor gel formation.
- Good flow properties and mould capabilities.
- No propensity for the drugs to form complexes.
- Possess a good mouth feel.
- Compatible with other excipients and have desirable properties in tableting.

Mechanism of Superdisintegrants (Roy, Bhowmik, & Kumar, 2014)[11]

Superdisintegrants acts in four major ways they are as follows:

Swelling

While not all effective disintegrating agents swell in interaction with water, swelling is known to be a process in which some disintegrating agents (such as starch) trigger disintegrating results. By swelling in contact with water, the adhesion to other materials in a tablet is resolved, allowing the tablet to break apart.

Porosity and capillary action (wicking)

The tablet in the aqueous media contributes to the penetration of the medium into the tablet and hence to the replacement of the adsorbed air resulting in the degradation of the intermolecular bond and the rupture of the tablet into fine particles.

Due to particle-particle repulsive forces

Electrical repulsive forces between particles responsible for disintegrating.

Deformation

On the tab. Compression, disintegrated particles are deformed when in contact with aq. Media is back to regular structure (Inc. in size).

By enzymatic reaction

Enzymes found in the body function as disintegrants. These enzymes disrupt the binding action of the binder and help to disintegrate. In fact, due to swelling, pressure applied in the outer direction or radial direction, it allows the tablet to burst or rapid absorption of water contributing to an immense increase in the volume of granules to facilitate disintegration.

Table 1: List of super disintegrants (Dhiman, Dev, & Prasad, 2022)[12]

Name of super disintegrants	Concentration (%)
Starch USP	5-20
Starch 1500	5-50
MCC(Avicel)	10-20
Alginic acid	1-5
Sodium Alginate	2.5-10
Explotab	2-8
Polyplasdone(XL)	0.5-5
Amberlite(IPR 88)	0.5-5
Ac-Di-Sol	1-3

Table 2 : List of natural superdisntegrants employed for different formulation development (Gandhi & Akhtar, 2019)[13]

Name of drug	Super disintegrants	Method of compression
Glimepride	Ocimum tenuiflorum	**Direct compression**
Lisinopril	Plantago ovate mucilage,aloe vera mucilage,hibiscus rosasinesis	**Direct compression**
Nimesulide	Lipidium sativum (Cruceferae)	**Direct compression**
Ondensetron HCL	Plantago ovate husk	**Direct compression**
Granisetron HCL	Plantago ovate husk	**Direct compression**
Fexofenadine HCL	Plantago ovate husk	**Direct compression**
Ofloxacin	Locust bean gum	**Solvent evaporation method**
Famotidine	Plantago ovate mucilage	**Non aqueous wet granulation**
Piroxicam	Treated agar	**Direct compression**
Metoclopramide	**Cassia fistula gum**	**Direct compression**

Table 3: List of synthetisuper disintegrantsts employed for formulation development (Gandhi & Akhtar, 2019)[14]

Name of drug	Super disintegrant	Method of compression
Solubutamol sulphate	Chitosan-alginate complex	**Direct compression**
Metaclopramide HCL	Cross povidone, Cross carmellose sodium	**Wet granulation**
Lornoxicam	Cross povidone, Banana powder, Soy polysaccharides	**Direct compression**
Lisinopril	Cross povidone, Cross carmellosesodium	**Kneading techniques**
Promethazine HCL	Cross povidone, Cross carmellose sodium, Sodium starch glycolate, pregelatinized starch, L-HPL	**Direct compression**
Acetaminophen	Cross povidone, Cross carmellose sodium, Sodium starch glycolate	**Wet granulation**
Efavirenz	Cross povidone, Cross carmellose sodium, Sodium starch glycolate	**Wet granulation**
Gliclazide	Cross povidone, Cross carmellose sodium, Sodium starch glycolate	**Direct compression**
Hydrochlorthiazide	Cross povidone, Sodium starchglycolate, Cross linked CMC, partially pregelatinized corn starch	**Direct compression**
Acetoaminophen and codeine phosphate	Cross carmellose sodium	**Direct compression**
Calcium carbonate	**Cross carmellose, Sodium starchglycolate, Cross povidone**	**Wet granulation**

Challenges in ODTs formulation development

Mechanical Strength and Disintegration Time

ODTs must have a shorter disintegration period in the oral cavity because they are composed of porous or soft-molded matrices or crushed with a low compression force, making the tablets brittle and challenging to handle. Only a few techniques, such as Wowtab and CIMA laboratories, can create sufficiently rigid and robust tablets to be packed in multi-dose bottles (Al-Khattawi & Mohammed, 2014).[15]

Taste Masking and Mouth Feel

As most pharmaceuticals are unpleasant to taste, therefore, drug taste masking is essential for patient compliance and acceptability, which is impacted when a bitter drug tablet dissolves in the oral cavity. Covering the taste of bittertasting drugs selected for ODT is challenging for formulation researchers. Larger particles should not disintegrate from ODT; instead, tiny particles with a pleasant tongue feel should disintegrate (Mahapatra, Swain, Revathi, Nirisha, & Murthy, 2013)[16].

Size of Tablet

Their size determines the degree of ease with which tablets are administered. It has been stated that the most superficial size of tablet to swallow is 7–8 mm, whereas the most accessible size to handle is one bigger than 8 mm.

As a result, producing a pill size that is easy to take and maintain is difficult (Litalien et al., 2022)[17].

Amount of Drug

The number of drugs that can be integrated into each unit dosage limits the applicability of ODT technology. The mass of the tablets should not exceed 500 mg, which is difficult to achieve when developing an ODT (Al-Khattawi & Mohammed, 2014)[18].

Hygroscopicity

Hygroscopic ODT does not maintain physical integrity at standard temperature and humidity settings; thus, they are shielded from humidity by a specific product container (Al-Khattawi & Mohammed, 2014)[19].

Good Packaging Design

At the outset, package design should be enhanced to prevent ODTs from the environment and humidity (Al-Khattawi & Mohammed, 2014)[20].

Conventional techniques of ODTs

Freeze-drying or Lyophilization

The process of eliminating the solvent from a frozen suspension or solution that contains medicine and other excipients is known as lyophilization. The drug is dissolved or distributed in an aqueous carrier solution. The mixture is pumped into the prefabricated blister pack wells. Liquid nitrogen is used to freeze the medication solution included in the blister packets. They are then placed in refrigerators to finish the freeze-drying process. Finally, the blisters are packed and sent to their destinations. Tablets that have undergone lyophilization are very porous, dissolve quickly, and have enhanced absorption and bioavailability. Humidity and higher temperatures will affect the lyophilized product of ODT. When put on the tongue, a lyophilized tablet will quickly dissolve. Compared to regular tablet pressing, freeze-drying is a more costly manufacturing method (Lai et al., 2014)[21].

Direct Compression

ODTs can be made using traditional tablet preparation processes, e.g., dry Granulation, wet Granulation, and direct compression. By limiting the number of processing stages, conventional compression apparatus with primary ingredients is employed. Rapidly disintegrating tablets are made using microcrystalline cellulose as well as low substituted hydroxyl propyl cellulose as a polymer. Rapid Disintegration can also be enhanced by applying CO_2 effervescent substance to the tablet, which effectively masks the taste of pharmaceutical ingredients. According to specific reports, high concentrations of super disintegrants have been used to provide good oral dispersibility with a pleasant feeling. Direct compression is cost-effective had many of the same advantages as traditional tablet manufacturing. It can sometimes include many disintegrants and hence have lower tablet hardness than conventional tableting methods (Aguilar-Díaz et al., 2009)[22].

Tablet Molding

This method is implemented for drug molecules dissolved in water or ethanol. The components are molded into tablets at a reduced pressure than traditional tablet compression force. By drying or evaporating, the solvent is eliminated. Molded Tablets have a porous structure, resulting in a rapid rate of disintegration (Rahane & Rachh, 2018).[23]

Effervescent Method

Effervescent ODTs are made by combining sodium bicarbonate with tartaric disintegrants such as sodium starch glycolate, cross povidone, and croscarmellose. To eliminate absorbed/residual moisture, sodium bicarbonate and tartaric acid were warmed at 80°C and well combined in the motor. The mixtures are finally crushed in the punch (Al-Khattawi & Mohammed, 2013).[24]

Sublimation

Subliming substances such as urea, camphor, ammonium bicarbonate, and hexamethylenetetramine are added to the other tablet component. Reduced pressure and temperature sublimate the volatile ingredient in a vacuum, leaving the tablets porous after production. When it comes to conventional kinds, fast Disintegration is not always the case (Sutradhar, Akhter, & Uddin, 2012).[25]

Spray Drying

Hydrated and non-hydrolyzed gelatins as supporting agents, mannitol as a bulking agent, and sodium starch glycolate/ croscarmellose as a disintegrant. A disintegration/dissolution agent such as citric acid and sodium bicarbonate can improve disintegration/dissolution. This technology is used to obtain quick dissolving (20 sec). However, it comes at a high cost and takes a long time to make, and it generates tablets with a meagre mechanical strength as well(Mishra, Bindal, Singh, & Kumar, 2006).[26]

Fast Dissolving Films

It consists of a non-aqueous solution comprising water-soluble film-forming polymers (pullulan, carboxymethyl cellulose, polyvinyl alcohol, or sodium alginate), a drug, and many other flavors masking ingredients, all of which are often used form a film after the solvent evaporates. Resin adsorbate or coated tiny particles of a medicine can be used in a film for bittertasting pharmaceuticals. These are thin films with a diameter of 22 inches that dissolve quickly in 5 seconds and leave a pleasant aftertaste (Gupta et al., 2010).[27]

Patented ODTs technologies

Flash Tab Technology

This Technology tablet has an active component in the form of microcrystals. Traditional methods such as coacervation, microencapsulation, and extrusion spheronization can create drugs in micro-granules. Tablets are made utilizing a shear form matrix that comprises fibrous polysaccharides that are compressed to produce thin sugar fibres that dissolve quickly when exposed to saliva. The tablets generated by this process are soft, brittle, humidity sensitive, and have a large surface area for dissolving, allowing them to dissolve in a matter of a few seconds (Patel & Gupta, 2013).28

Zydis Technology

Zydis is a one-of-a-kind freeze-dried tablet that has the pharmaceutical physically trapped or dissolved inside a matrix of quickly dissolving carrier material. When patients put zydis pills in their mouths, the freeze-dried structure rapidly disintegrates, and they do not need water

to consume them. The zydis matrix comprises a mix of components that collaborate to achieve various objectives. Polymers such as gelatin, dextran, or alginates add strength and resilience during handling. These combine to produce a glossy amorphous structure that adds stability. Zydis pharmaceuticals are wrapped in blister packs to preserve the formula from environmental dampness(Nayak & Manna, 2011).[29]

Orosolv Technology

Traditional blenders and tablet machines are utilized, but a low compression force is used to speed up the tablet's oral Disintegration. Because Orasolv tablets are more brittle than traditional dose forms, CIMA, the company that makes them, devised a specific handling and packaging approach to compensate (Jassem, 2022).[30]

Wowtab Technology

Yamanochi Pharmaceutical Company has patented this technique, and WOW stands for "Without water." Two distinct types of saccharides are used in the preparation of the WOW tab, such as saccharides with high moldability and hardness (maltose, mannitol, and sorbitol), are mixed with limited moldability saccharides (lactose, glucose, mannitol, xylitol) and compressed to produce a tablet formulation with appropriate hardness and quick-dissolving rate (Nayak & Manna, 2011).[31]

Oroquick Technology

The Ora Quick fast-dissolving/disintegrating tablet formulation uses a unique flavour masking technique. Microsphere technology, known as Micro Mask, offers a better mouth feel than other taste-masking options. The flavor masking method does not use any solvents, resulting in quicker and more effective production. Also, because Ora Quick produces less heat than other fast-dissolving/disintegrating technologies, it is suitable for heat-sensitive drugs. Because the matrix surrounding and protecting the pharmaceutical powder in microencapsulated particles is more flexible, tablets may be compressed to produce substantial mechanical strength without interfering with flavor masking (Manivannan, 2009).[32]

Characterization of ODTs

Hardness

The tablet is broken by applying force across the width of the tablet. The hardness of 10 tablets from each formulation is measured using a Pfizer hardness tester. The tablet is put on a hardness tester to determine the force necessary to break it. To aid rapid breakdown in the mouth, the mechanical strength of ODTs is limited to the lowest range (Gryczke, Schminke, Maniruzzaman, Beck, & Douroumis, 2011).[33]

Wetting Time

The shorter the wetting time, the faster the pills dissolve. To determine the wetting time, five circular tissue sheets with a diameter of 10 cm are placed in a Petri dish. Ten millilitres of water-soluble dye, such as eosin solution, are placed in the Petri plate. On the tissue paper's surface, a tablet is softly placed. The wetting time is the length of time it takes for water to reach the tablet's top surface. To establish the water-absorption ratio, the weight of the tablets before they are placed in the Petri dish is recorded (Wb). The wetted tablet from the Petri dish is begun taking and reweighted (Wa). The water-absorption ratio, R, can be calculated using the equation below (Sutthapitaksakul, Thanawuth, Huanbutta, & Sriamornsak, 2022):

$R = 100 (Wa - Wb)/Wb.$

Friability

The Roche Friabilator, which is used to measure tablet friability and is reported as a percentage, is used to estimate hardness also. The range is 0.1–0.9% in all aspects. Initially, ten pills were weighed, placed in a friabilator, and spun at 25 rpm for 4 minutes before being reweighed. The acceptability value was computed using the pharmacopoeia employed to measure friability, the loss in tablet weight due to abrasion (Vlad et al., 2022).

Moisture-uptake Studies

In this investigation, the tablets' stability is evaluated. Ten tablets were kept in desiccators over calcium chloride at 37°C for 24 hours. For two weeks, weighted tablets were subjected to 75% relative humidity at room temperature. Desiccators were filled with a saturated sodium chloride solution for three days to produce the required moisture. One tablet was retained as a control (without super disintegrant) to measure the moisture absorption due to the formulation's other excipients. The % increase in weight of the tablets is observed (Ghourichay, Kiaie, Nokhodchi, & Javadzadeh, 2021).

Disintegration Test

The disintegration test device was used to determine the in-vitro disintegration time. The disintegration duration of ODTs is the essential feature since they must break down in a minimal amount of saliva in a brief period, typically 1 minute. One tablet is placed into each of the apparatus's six tubes. The conventional technique for performing disintegration tests has numerous drawbacks for these dosage formulations. Researchers began to look for alternative tests because there was no ODT-specific disintegration test. According to assumptions, the disintegration test for ODTs is intended to imitate the Disintegration in the mouth within salivary contents (Ghourichay et al., 2021).

Dissolution Test

Since ODTs dissolve quickly, the FDA advises using apparatus two at a speed of 25–75 rpm to assess drug dissolution of ODTs. In contrast, apparatus one will be used at a rate of 50 rpm/min. Selecting media to portray in vivo media is one of the most challenging tasks. Studies have suggested various mediums to simulate dissolving in the oral cavity. The usage of Simulated Saliva (S.S.) is one of the mediums utilized for this (Fouad, Malaak, El-Nabarawi, & Abu Zeid, 2020).

Industrial applications of ODTs (Agiba & Eldin, 2019)

- To develop an orally disintegrating dosage forms and to work with existing disintegrants.
- To further improve upon the existing technology of ODTs.
- To optimize the blend of disintegrants or excipients to achieve ODTs.
- To select and develop proper packaging material and system for enhanced stability of the product and also develop a cost-effective product.

- To arrive at different taste-masking agents and prepare palatable route of administration thereby increasing patient compliance.
- To develop disintegrants from different polymers which are used as coating materials by certain modifications and use them for formulating ODTs.

Future Prospects

These dosage forms may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that has limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. The next generation drugs should be peptide based or predominantly protein, tablet may no longer be the dominant format for dosing such moieties. Injections generally are not preferred for use by patients unusually facilitated by twist auto injectors. Inhalation is one of the correct approach systems to deliver these drugs, but the enhanced research into biopharmaceuticals so far has generated predominantly chemical units with low molecular weights. The developments of enhanced oral protein delivery technology by ODTs which may release these drugs in the oral cavity are very encouraging for the delivery of high molecular weight protein and peptide (Patoliya, Joshi, & Upadhyay, 2021).

Conclusion

ODTs are one of the most promising novel drug-delivery techniques. ODTs can be more effective than traditional solid dose forms. When delivered, a fast-dissolving tablet behaves as a solid dose form when outside the body and as a solution when within the body. As a result, patient compliance, convenience, bioavailability, and time to action have all improved. Because of its lack of mechanical strength, this dosage form should be handled with caution. Many more types of drugs might be produced using ODTs in the future. This technology is mostly used for drugs to treat mental disorders, anti-allergic and analgesics. Dysphagia is also one of the major problems which were dealt with the invention of this novel drug delivery system. ODTs are the novel delivery system that has various advantages over conventional drug delivery in aspects of improved patient compliance, bioavailability and rapid onset of action. ODTs dissolve/disperse in saliva and can be administered without the need of water. The basic approach in the ODTs technology is the maximize the porous structure of the tablet matrix to achieve rapid disintegration in the oral cavity & also provide excellent mouth feel, good taste masking properties of bitter drugs and good mechanical strength. Intensive investigation is much needed in this promising area which can result in better result of newer cost-effective technologies and improved excellent products.

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