WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 17, 288-308. Review Article ISSN 2277–7105

FORMULATION AND QUALITY CONTROL OF ORALLY DISINTEGRATING TABLETS (ODTS): RECENT ADVANCES AND PERSPECTIVES

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Article Received on
12 July 2024,

Revised on 01 August 2024,
Accepted on 22 August 2024

DOI: 10.20959/wjpr202417-33721

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ABSTRACT

The 1980s saw the introduction of ODT technologies' products to the market, which have since seen a steady increase in demand and a quick expansion of their product streams. Without the need for water, oral disintegrating tablets (ODTs) dissolve or quickly disintegrate in the oral cavity. In both academia and the pharmaceutical business, there is a growing demand for ODTs. ODTs are said to provide a number of benefits over other traditional tablets. When saliva travels down into the stomach, some of them are absorbed from the mouth, throat, and esophagus, which significantly increase the drug's bioavailability. In addition, ODTs' instantaneous release characteristic makes them a well-liked oral dose form for kids, adults, and patients who require a quick start of action. The characteristics of the excipients and active substances utilized in the formulation of ODTs are described in the current review paper. This gives solutions for issues related to ODTs and addresses several ODT formulation and preparation methods, each having pros and cons. additionally, necessary concerns and quality control procedures are provided.

KEYWORDS: Oral Disintegrating Tablets (ODTs), Quickly Disintegration, Oral cavity, Instantaneous Release.

1. INTRODUCTION

In the pharmaceutical business, oral drug administration is now the gold standard as it is seen to be the most patient-compliant, cost-effective, and safest mode of drug delivery.[2] The most favored method of administration is oral, and the most popular dose forms are tablets and capsules. However, there are a few drawbacks to this type of dosage form, including swelling pain and choking in elderly and juvenile patients.[2]

As a delivery strategy, the orally disintegrating tablet (ODT) breaks down quickly in the mouth when it comes into contact with saliva; consequently, it doesn't require extra water. It can be absorbed through the mucosa of the pregastrium.This type of dosage form has also been known as mouth dissolving/disintegrating tablets (MDTs), quick disintegrating tablets, fast/rapid dissolving or disintegrating tablets (FDTs), quick/rapid melt tablets, orodispersible tablets, and porous tablets.[3] Orodispersible pills disperse quickly in the mouth before swallowing and are uncoated. Orodispersible tablets disintegrate within 180 seconds when disintegration tests are completed up to the test for tablet disintegration.[4]

In particular for paediatric, geriatric, psychiatric, paralysed, and bedridden patients, the need for quick disintegration, quick onset of action[5], and patient compliance led to the development of OTDs in the 1980s and the publication of the first papers on the formulation of ODTs using cellulose derivatives by Watanabe etal. ODTs are described as "a solid dosage form containing medicinal substances which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue" by the Food and Drug Administration (FDA). By contrast, they are described as “uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed and as tablets which should disintegrate within 3 min” in the European Pharmacopoeia (Ph. Eur.). ODTs are not defined in the United States Pharmacopoeia (USP), despite the fact that they are addressed in several USP monographs.[7]

Ondansetron ODTs, for example, were safely delivered to children while reducing the incidence of emesis. Furthermore, preventing first-pass metabolism in ODTs increases bioavailability, which reduces side effects and dosage frequency.[8] Dysphasia, a disorder characterized by difficulty swallowing, has been linked to noncompliance and inadequate therapy. These conditions include motion sickness and allergic reactions. In these situations, ODTs will improve comfort and quality of life. One further benefit of ODTs is their affordable treatment. Olanzapine and risperidone ODTs were shown to be more cost-effective and efficient in treating schizophrenia than standard oral tablets (SOT) based on statistical

studies.[9] Additionally, for Chinese patients with schizophrenia, aripiprazole ODTs proved to be more economical than aripiprazole SOTs and olanzapine SOTs.[10]

Claritin (loratadine) was initially approved by the US Food and Drug Administration (FDA) in December 1996 through the Zydis ODT formulation. It was succeeded by the Zydis ODT formulations of Maxalt (rizatriptan) in June 1998 and Klonopin (clonazepam) in December 1997.[11]

Clinical categories with the most potential for ODTs: according to 2004 estimates, three therapeutic areas account for 92% of the global ODT market. These are the digestive system (29%) and oncology (13%), with the central nervous system holding a 50% market share. Treatments for gastro esophageal reflux disease (GERD), pain, Parkinson's disease, schizophrenia and other central nervous system (CNS) disorders, migraine, nausea, and sleeping pills have the best chance of working with ODTs.[2]

Technology Catalysts International[2] estimated the global ODT market to be worth $2.4 billion in 2004 based on sales to wholesalers straight out of the facility.

Features and Excepients

There are more systemic than local effects with most APIs utilized in ODT formulations.Some variables that can affect the final ODT features include a drug's solubility, crystal shape, particle size, hygroscopicity, and compressibility, but these should have little effect on tablet quality. The medications that are most commonly manufactured as ODTs include analgesics, antihypertensives, anti-inflammatories, antibacterials, antifungals, and antilipidemics.

In order for ODTs to be considered an appropriate and perfect dosage form, a medicine must meet a number of requirements. To ensure no residue is left in the oral cavity, the medicine should, for instance, be ionized, distributed, and permeate all mucosa. Moreover, less than 500 da should be the molecular weight of the API.[12] For regular usage, the active compound should have a short half-life, a nice taste, and a pleasant scent, with less than 50 mg. The industry and patients find them even more enticing due to their low production costs, resistance to extreme environmental conditions, and compatibility with current processing and packaging techniques.[13][14]

Table 1: ODT formulations available for purchase.

Product	Active substance
Benadryl®	Diphenhydramine
Claritin® RediTabs®	Loratadine
Alavert®	Loratadine
Zomig®	Zolmitriptan
Tempra®	Acetaminophen
NuLev.	Hyoscyamine
Ultram®	Tramadol
Excedrin®	Acetaminophen, aspirin
Maxalt®	Rizatriptan
Zyprexa®	Olanzapine
Pepcid RPD	Famotidine

Excipients must meet specific conditions, including being water soluble, having a pleasing taste, being sweet, and dispersing quickly, because they are also essential to the formulation of ODT.[14] Various processed excipients, such Ludiflash, Pharmaburst, F-melt, and modified chitosan are used to improve formulations and reduce material wasteaddress issues like palatability, flowability, hygroscopicity, compressibility, disintegration, and dissolution. The SeDeM expert system is used to create these excipients, and it considers a number of factors while evaluating excipients in order to determine which powder characteristics are appropriate for achieving before compression.[15,16] While mannitol and other modified excipients are employed as diluents, their changed form possesses numerous additional advantageous properties such as greater stability, larger pore size, and increased total surface area, all of which contribute to the creation of a product that is ultimately more affordable.[17]

Table 2 enumerates the excipients required for an OTD preparation along with their function in the formulationSuperdisintegrants are gas-evolving disintegrants (sodium bicarbonate, citric acid, and tartaric acid) and ion exchange resins (indion 414/234, tulsion 234/344, and amberlite IPR 88). Cross povidone is the most compactable and fibrous of these disintegrants, although sodium starch glycolate flows well. Sugar and sugar-based compounds that are highly water soluble and sweet are used as bulking agents and sweeteners.

Table 2: These are some approved excipients in formulations.

Ingredient type	Example	Role	Ref.
Superdisintegrant	spray-dried lactose, acrylic acid, alginic acid, sodium alginate, soy polysaccharides, modified corn starch, ion exchange resins, croscarmellose sodium, sodium starch glycolate, sodium carboxymethyl cellulose, microcrystalline cellulose and isphagula husk pregelatinized starch.	(i) Burst disintegration facilitator	[18]
Bulking material	Sugar and sugar-derived products (such as lactilol, polydextrose, xylitol, fructose, isomalt, maltitol, maltose, mannitol, sorbitol, and starch hydrolysate).	Improves textural qualities (disintegration time).	[20]
Emulsifier	fatty acid esters (Tweens), sodium lauryl sulphate, sodium dodecyl sulphate, propylene glycol, lecithin, sucrose esters, and polyoxyethylene sorbitan fatty acid sulphate	(i) Disintegration accelerator (ii) Bioavailability enhancer of immiscible substances	[21]
Sweetener	Sodium saccharin, sugar alcohols, natural sugars (sugar, dextrose, fructose), sugars derivatives, aspartame, vanilla, bubble gum, grapefruit	(i) Bitter taste mask (ii) Tablets' acceptability enhancer	[19]
Flavor	peppermint flavour, clove oil, bay oil, anise oil, eucalyptus oil, thyme oil, bitter almond oil, vanilla, citrus oils, and fruit essences.	i) Increases patient compliance and acceptability.	[22]

The Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Medicines Agency (EMA), the Committee for Human Medicinal Products (CHMP), the International Conference on Harmonisation (ICH), the European Food Safety Authority (EFSA), and indexed literature should all be consulted when determining the safety of excipients prior to formulation.[23,24]

Aside from that, before choosing excipients, the drug-excipient compatibility should be studied. The interactions between API and excipient that could occur are thought to be physical, chemical, and biopharmaceutical. A poor choice of excipients may result in premature breakdown of the enteric coat, interactions from adjunct medication (such as the creation of a complex between tetracycline and calcium), and increased gastrointestinal motility (from sorbitol and xylitol).[25]

2. METHODS USED TO PREPARE ODTS

Various methods for preparing the ODT tablets are as follows.

Molding

ODTs made using a molding process break down in five to fifteen seconds. Heat molding and compression molding are the two categories into which molding, or solid dispersion, may be

divided. Molded tablets are made from a molten substance that contains a medication that has been dissolved or scattered.[26] First, the drug is suspended in agar with water-soluble carbohydrates such mannitol, lactose, sucrose, glucose, sorbitol, or xylitol. These sugars have the dual purpose of binding and increasing mouthfeel. After pouring the suspension into blister packs and moulds, the solvent is forced to evaporate under vacuum at 30°C, hardening the agar solution and generating ODTs. A powder blend is mixed with a hydroalcoholic solvent and squeezed into mould plates with minimal force. The tablets are then air-dried to release their solvent and form a porous structure with a high rate of disintegration and dissolution. This procedure is used to create ODTs for valdecoxib and perphenazine.[27,28] The primary drawbacks of this method are its expensive cost of manufacture and poor mechanical strength, which causes ODTs to shatter when handled roughly when blister packs are opened. To get around this problem, binders including PEG, acacia, and polyvinylpyrrolidone may be used.[29, 30]

Fig -01- Representing the Molding process.

Extrusion in Mass

The mass extrusion procedure uses water-soluble solvents, such as PEG and methanol or ethanol, to soften the powder combination. Following that, it is syringed or sieved through an extruder. Evaporation was employed to remove alcohol after extrusion. A gel that resembles string solidifies and is then crushed into granules with a mortar. These granules might then be mixed with other chemicals and compacted using the processes described in the next sections to form ODTs.[31] PEG stearate serves as a binder in mass extrusion, increasing physical strength and disintegration. By coating granules with substances like Eudragit E 100, ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyvinyl alcohol, and polyvinyl acetate, it is possible to disguise the harsh taste of the medication using this approach.[32]

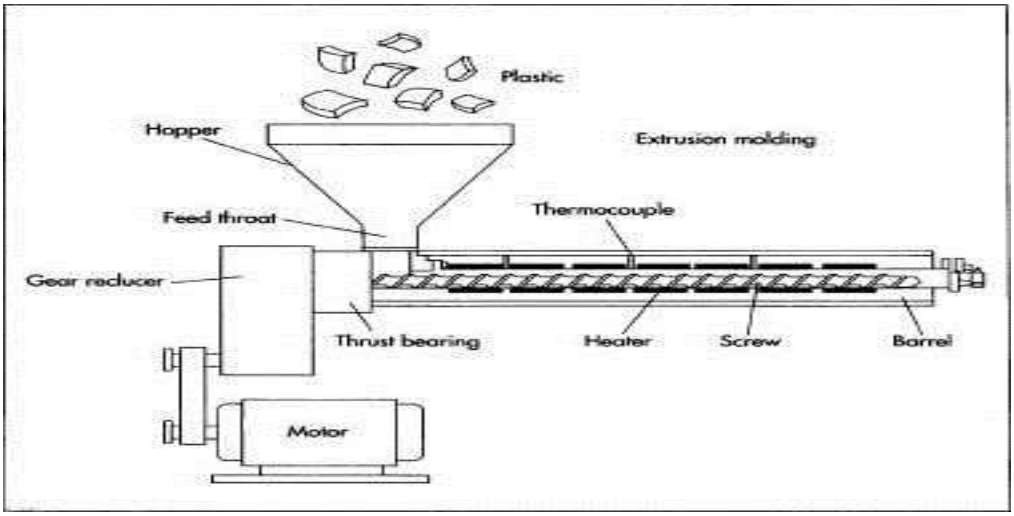

Fig -02: Representing the Mass of Extrusion.

Spray Drying

Spray-drying is a common method for producing solid dispersions and micronised drug/excipient particles for oral or inhalation delivery.[33] To make a highly porous structure, a liquid mixture of components is sprayed into a heated chamber. These microparticles were commonly mixed with mannitol and kneaded with distilled water before being dried at 60°C for two hours. The resulting granules were sieved, mixed with additional excipients, and compacted into tablets using the processes described in the next sections. This method creates tablets with high porosity that dissolve quickly in the mouth.The fragility of the product and the high cost of manufacture are the main drawbacks of this procedure, which renders standard packing techniques inadequate for this dose.

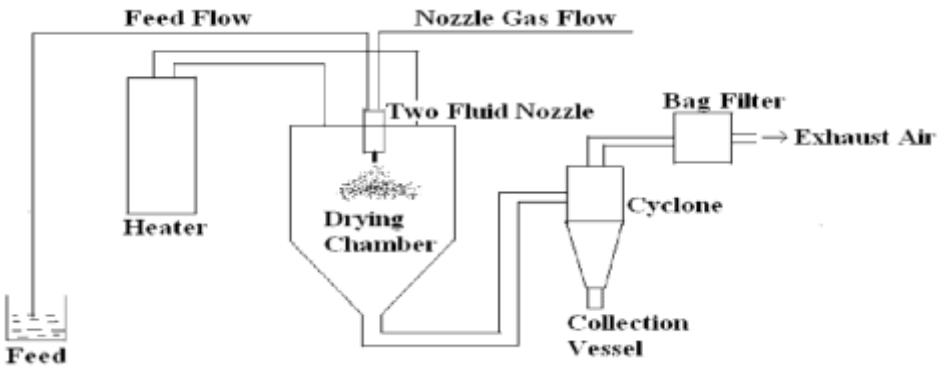

Fig 03: Representing the Spray drying.

Freeze-drying or lyophilization

The process of lyophilization involves using a vacuum to dry thermosensitive APIs at a low temperature. A common term for freeze-dried ODTs is lyophilizates. They often break down

quickly, have extremely porous structures, and are very light. Accurate dosing is achieved by formulating freeze-dried OTDs in a liquid condition. Moreover, it is safer for operators to handle strong or poisonous APIs in a liquid form rather than a powdered form. Nevertheless, the procedure is somewhat expensive and inappropriate for formulations that degrade at elevated temperatures and humidity levels.[35,36]

Lyophilization is carried out using two platforms: Lyoc and Zydis. The Zydis process begins with the production of an aqueous bulk liquid containing mannitol as a mechanical booster and gelatin as a polymeric binder. In the completed ODT, gelatin acts as a glue, holding API and filler particles together. Furthermore, the addition of a hydrophilic filler, such as mannitol, which is highly soluble in water, may help the disintegration process.[37] Preservatives, flavour masking agents, colourants, and pH modifiers can all be added to the combination. Following its placement in blister pockets, the liquid composition is swiftly frozen using a tunnel freezer. Blisters are transported to large industrial batch freeze-dryers for vacuum-assisted main and secondary drying once they have completely frozen. Blisters are sealed and stored once they have dried.

Zydis has some drawbacks. To start, intrabatch pore-size heterogeneity is caused by inconsistent hardening time in the semicontinuous freezing mode.[38] Second, some individuals cannot consume animal products such as gelatin due to ethical concerns; also, the quality of gelatin varies and its viscosity is affected by temperature, pH, and time.[39] As an alternative to gelatin, polyvinyl alcohol (PVA) has been investigated and documented. As xanthan gum does not prevent drug sedimentation during the initial freeze-drying step, it was chosen as a viscosity enhancer. Raman spectroscopy may be used to quantify sedimentation, and xanthan gum content could be adjusted to decrease it.[39]

During manufacturing, the glassy amorphous structure needs polymers like gelatin, dextran, and alginate to provide it stability and flexibilityFor example, gelatin and sodium alginate were utilised to make a matrix and viscosity modifier in the manufacture of terbutaline sulfate ODT. The filler employed in the formulation was mannitol, which provides freeze-dried ODTs their crystallinity and hardness. Other ingredients were hydroxypropyl methylcellulose, pluronic F68 (a surfactant to increase TBS's poor solubility), and PEG 4000 (as a disintegration accelerator). Moreover, as shape variation may result from foaming during the mixing process, simethicone was used as an antifoaming ingredient to produce homogenous ODTs.[40]

With Lyoc technology, water-soluble fillers like lactose or mannitol are used to create an oil-in-water emulsion. When a lot of fillers are used, the formulation eventually becomes paste-like and sedimentation is prevented. Then, commercial freeze-dryers are used for the freeze-drying stages, similar to the Zydis method.[41] Because of its low porosity and longer drying time, the Lyoc approach was less effective.

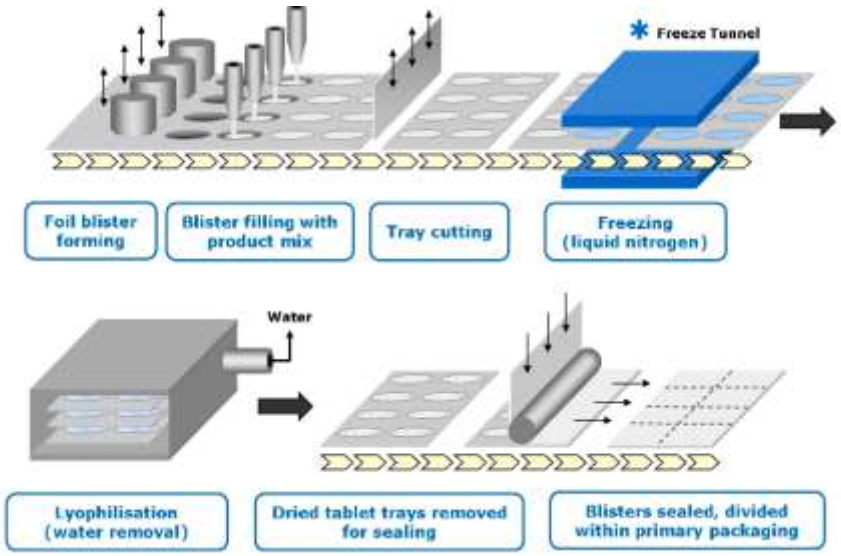

Fig. 04: Representing the Freeze-drying or lyophilization.

Compaction Methods

During this procedure, integrated structures like tablets or briquettes are prepared using a compression device that applies pressure to encourage particle agglomeration and bonding. Tablet size, APIs, and excipient characteristics all affect the applied compression force. For instance, compressive force in the range of 3 to 8 kN should be used in the formulation of ODMTs, according the research of Stoltenberg and Breitkreutz.[42] The choice of excipient is also important because compression reduces the product's porosity, which is important for fast disintegration; this issue demands for the use of super disintegrates and sugar-based fillers.[43, 44] Compaction can be achieved by a variety of methods, from serial devices like extrusion to limited compression devices like tabletting. The compaction approach forms the basis for the subsequent techniques.

Sublimation

In addition to other excipients, sublimation process, medications, and a quickly volatilised element Urea, camphor, menthol, ammonium carbonate, ammonium bicarbonate, benzoic acid, hexamethonium tetramine, naphthalene, phthalic anhydride, and urethane were all used.

Sometimes, additional porosity was increased by using solvents like cyclohexane/benzene. After compressing the produced blend into a tablet shape, pressure and heating are used to evaporate the volatile substance, causing the residual bulk to become porous. The key component of tablets made using the sublimation procedure is their high porosity. Moreover, complicated procedures like the sublimation of frozen water are eliminated by the volatilisation of volatile material. Angiotensin-converting enzyme inhibitors like captopril are used to treat acute hypertension, and following oral administration, the drug is expected to take full effect 1-2 hours later.[45]

Melt Granulation

This method employs a binding material with a low melting or softening point and avoids the use of solvents or a drying process. Melted components act as a binder for a solid dosage form, which solidifies at room temperature. The waxy binder is melted within the mixer to make granules, which are subsequently dried using tray dryers. The uniformly sized granules are obtained by sifting, after which they are combined with additional substances and crushed into tablets. Melt granulation produces cost-effective, controlled-release particles. Hasian produced ODTs with melt adsorption particles by optimising the manufacturing parameters. As the adsorbent, they used Neusilin US2 to make melt adsorption particles.[47]

Phase Shift

This procedure involves compressing the powder, which contains two forms of sugar alcohol with different melting points, and then heating the compacted bulk to a temperature between the two melting points. Kuno et al. used this procedure to make ODTs because low compressibility and enhanced interparticular bonding lower hardness, but heating increases hardness due to sugar alcohol diffusion and solidification. Low compression force is followed by a humidity or heat treatment to increase mechanical strength throughout the phase transition method in order to retain porosity, however heat or humidity may affect the stability of water-sensitive or thermolabile drugs.[46]

3. QUALITY CONTROL TESTS FOR ODTS

With a few minor exceptions, the quality control tests of ODTs are identical to those of regular tablets. Examples of metrics that are specifically utilised for ODTs include wetting time, Moisture absorption, in-vivo disintegration time, and flavour evaluation. Precompression and postcompression testing are the two categories into which quality control tests are separated.

Precompression Tests

Precompression studies are performed on the powder combination used in ODT manufacture. These tests include calculating the angle of repose, bulk density; tapped density, Hausner ratio, and Carr's index.[52] Precompression investigations are conducted to make sure the powder has the appropriate properties for further processing.

Frictional force in a loose powder is demonstrated by the angle of repose. For a particular powder, a slope less than 30 indicates free-flowing behaviour. The Hausner ratio and Carr's index, respectively, show the flow tendency and compressibility. Accordingly, flowability is favourable when the Hausner ratio is less than 1.25, and great compressibility is observed when the Carr's index is less than fifteen.[52] Bulk Density is useful for choosing packing materials and transportation considerations because it is directly related to particle size and adhesive propensity.

Post compression Tests

The final ODTs are subjected to postcompression testing. The weight fluctuations, hardness, thickness, friability, wetting duration, water absorption ratio, and moister uptake are among the tests that are indicated in Table 3.

In vitro methods for determining disintegration time

To be distributed throughout the patient's oral salvia, ODTs need to be easily crushed. In addition, they must be strong enough to withstand the mechanical strain of shipping and production. A disintegration time test must be performed in both in vitro and in vivo settings in order to ascertain this quality.[57] Ölmez and Vural conducted a detailed review of in vitro disintegration time experiments. They identified five tests to assess the start and end points of disintegration: the Ph. Eur. approach, texture analysis method, charge-coupled device (CCD) camera method, rotary shaft method, and a modified USP method.

Additionally, the Aston test was presented by Koner et al. in a recent study as a revolutionary disintegration technique that can replicate the oral cavity's environment.[57] They contrasted their system with the USP approach in their study. They demonstrated that the Aston test could distinguish between various ODTs with short disintegration times and between ODTs and immediate-release tablets. Additionally, it showed a linear in vitro/in vivo correlation (IVIVC)when compared to the USP test's "hockey stick" profile. All things considered, they

came to the conclusion that their test is a reliable way to evaluate ODT disintegration time in the pharmaceutical and oversight industries.[57]

Ph. Eur states that one ODT was inserted into three of the basket-rack assembly's six cylinders. After that, the device oscillated 31 times per minute in a 37°C, 900 mL water bath. Every ODT type must fully dissolve within three minutes in order to be deemed successful, and the time it takes for each tablet to do so is timed.[60] Similar to this, tablets are positioned and suspended in the centre of USP apparatus II's container (900 mL, 100 rpm, 37°C) in the modified USP dissolving test. Disintegration time was defined as the amount of time required for a tablet to completely dissolve and pass through a sinker's sieve.[61] In contrast, a tablet attaches to a probe in a texture analysis instrument. It is then pushed towards the base of a beaker filled with distilled water by a steady pressure, and the degree of penetration is determined.[62] One technique for texture analysis that is reminiscent is the rotating shaft method. ODT is positioned on a perforated plate in this test, and mechanical stress is applied by the rotating shaft. The end of disintegration is then detected by an electrical sensor.

With the CCD camera approach, two steel containers—an external thermostat and an inside container holding 200 mL of distilled water—are used to carefully regulate the temperature. A CCD camera records images, which are then transferred to a computer that has motion capture software installed. Image analysis software is then used to calculate the disintegration time. This approach allows for the identification of subtle differences between various ODT formulations since disintegration takes place in a medium that is only slightly stirred. Furthermore, it offers qualitative data such as the morphological modifications made to the tablet during disintegration.

As previously stated, the Aston test was developed lately and is designed to replicate oral cavity circumstances. The test is conducted with a hot plate and potassium chloride to replicate an in vivo environment with a temperature of 37 ± 1°C and relative humidity of 93 ± 3%RH. A silicone pipe with 4 mm pores that has been gently flattened serves as a disintegration bed. A texture analyser is used to quantify the disintegration of the tablet caused by the media's interaction with it and a flow of water (10 ml/min) through the pores that mimics saliva.[63] Disintegration time was determined using the distance/time plot for each of the eight tests.

In Vivo Determination of Disintegration Time, Taste, and Mouthfeel

In addition to the in vitro disintegration test, ODT is used for in vivo disintegration and taste evaluation.[58] Disintegration time can be measured in vivo using a random sample of healthy participants. First, mouthwash is requested of the volunteers. After placing a pill on their tongue, the amount of time it takes for the final granule to dissolve will be calculated. It is necessary to obtain prior clearance from the Board of Ethics if tablets contain active ingredients that cause negative effects in healthy volunteers.

When creating medications with bitter tastes, flavour masking is a crucial step that must be taken; otherwise, patient compliance may be difficult to achieve. The most popular method for getting rid of the bitter flavour is to add sweeteners like sugar. Another helpful method that is suggested is pH adjustment.[64] If these techniques proved ineffective in enhancing the flavour, it may be necessary to restrict the amount of interaction between the API and taste buds by incorporating physical barriers, such as coating the API particle or enclosing it inside substances like cyclodextrin.[65,66] Because coating material application can change a drug's biopharmaceutical behaviour, it must be carefully considered.Other formulation techniques that improve solubility beyond flavour masking include solid dispersions, hot-melt extrusion, and nanotechnology.[56,67,68]

DISSOLUTION TEST

Because it can be used to obtain the drug-release profile, this test is crucial. You can use both of the USP dissolution test devices. Orodispersible pill dissolution happens quite quickly. A USP 2 Paddle-type apparatus with a speed of 50-100 r/min is used for dissolution testing. Swammy et al. conducted an in vitro dissolving study using 900 ml of pH 6.8 at 37 ± 0.5°C as a dissolve medium for pheniramine maleate orodispersible tablets in a type II apparatus with r/min 550.When it comes to orodispersible tablets, the USP type I basket apparatus can be useful, although bits or fragmented tablet masses may become caught on the inside top of the basket at the spindle. The FDA requires that at least 85% of the API in ODTs be dissolved within 30 minutes. UV-Vis spectroscopy and high-pressure liquid chromatography (HPLC) are commonly employed to determine the amount of dissolved API.[68]

Packaging Consideration

One of the most important phases in the creation of an ODT is packing. Excipients used in the formulation of ODTs should dissolve or disintegrate in the least amount of water; nevertheless, they may also draw moisture from the environment, therefore great care must

be taken when storing them, such as in a dry location. Furthermore, ODTs made using various methods require variable packing because their mechanical strengths vary.[68] Zydis, for instance, created porous ODTs that are less sensitive to moisture and have less physical resistance.

4. CONCLUSION

In conclusion, orally disintegrating tablets (ODTs) represent a significant advancement in pharmaceutical dosage forms, offering notable benefits such as improved patient compliance, enhanced bioavailability, and suitability for individuals with swallowing difficulties. However, challenges such as moisture sensitivity, taste masking, and the complexity of formulating with certain active ingredients continue to pose obstacles. Recent innovations, including novel formulation techniques, controlled-release technologies, and advanced excipients, are paving the way for overcoming these limitations and enhancing the efficacy and appeal of ODTs. As ongoing research addresses these challenges, ODTs are poised to offer increasingly effective and patient-friendly solutions in the pharmaceutical landscape. The continued development and optimization of ODT technologies will likely lead to broader applications and improved therapeutic outcomes, ensuring that they meet the diverse needs of patients and healthcare providers alike.

5. REFERENCES

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8719989/
2. Abay FB, Ugurlu T. Orally disintegrating tablets: a short review. Journal of Pharmaceutics & Drug Development, 2015 Jun 25; 3(3): 303.
3. Cantor S. L., Khan M. A., Gupta A. Development and optimization of taste-masked orally disintegrating tablets (ODTs) of clindamycin hydrochloride. *Drug Development and Industrial Pharmacy*, 2015; 41(7): 1156–1164. doi: 10.3109/03639045.2014. 935392. [PubMed] [CrossRef] [Google Scholar] [Ref list]
4. Nagar P, Singh K, Chauhan I, Verma M, Yasir M, Khan A, Sharma R, Gupta N. Orally disintegrating tablets: formulation, preparation techniques and evaluation. Journal of Applied Pharmaceutical Science, 2011 Jun; 30(Issue): 35-45.
5. Doenicke A., Melchart D., Bayliss E. Effective improvement of symptoms in patients with acute migraine by GR43175 administered in dispersible tablets. *Cephalalgia*, 1989; 9: 89–92. [PubMed] [Google Scholar]

6. Watanabe Y., Koizumi K., Zama Y., Kiriyama M., Matsumoto Y., Matsumoto M. New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. *Biological and Pharmaceutical Bulletin,* 1995; 18(9): 1308–1310. doi: 10.1248/bpb.18.1308. [PubMed] [CrossRef] [Google Scholar]
7. *European Pharmacopoeia*. 10. Strasbourg: C.o. E, 2019. [Google Scholar]
8. Mostafa M., Gardouh A. R., Abogresha N. M., Gad S. Factorial design, formulation, in vitro and in vivo evaluation of rapid orally disintegrating tablets prepared by sublimation technique using captopril as a model drug. *Journal of Drug Delivery Science and Technology,* 2020; 57, article 101635 doi: 10.1016/j.jddst.2020.101635. [CrossRef] [Google Scholar]
9. Ascher-Svanum H., Furiak N. M., MS, Lawson A. H., MA, et al. Cost-effectiveness of several atypical antipsychotics in orally disintegrating tablets compared with standard oral tablets in the treatment of schizophrenia in the United States. *Journal of Medical Economics,* 2012; 15(3): 531–547. doi: 10.3111/13696998.2012.662923. [PubMed] [CrossRef] [Google Scholar]
10. Lin Z., Xuan J. Cost-effectiveness of aripiprazole orally disintegrating tablets in the treatment of schizophrenia in China. *Expert Review of Pharmacoeconomics & Outcomes Research,* 2020; 20(5): 549–557. doi: 10.1080/14737167.2020.1807331. [PubMed] [CrossRef] [Google Scholar]
11. Jain D,Amul M (2014) a review – formulation and development of orodispersible tablet. Int j pharm eru, 4: 21-38.
12. Rahman Z., Zidan A. S., Khan M. A. Risperidone solid dispersion for orally disintegrating tablet: its formulation design and non-destructive methods of evaluation. *International Journal of Pharmaceutics,* 2010; 400(1-2): 49–58. doi: 10.1016/j.ijpharm.2010.08.025. [PubMed] [CrossRef] [Google Scholar] [Ref list]
13. .Sharma S., Bhardwaj P., Gupta G. Formulation, evaluation and optimization of mouth dissolving tablets of losartan potassium: effect of coprocessedsuperdisintegrants. *International Journal of Pharma and Bio Sciences,* 2010; 1(1): 76–83. [Google Scholar]
14. Gunda R. K., Kumar J. N. S. Formulation development and evaluation of amisulpride fast dissolving tablets. *Fabad Journal of Pharmaceutical Sciences,* 2018; 43(2): 15–25. [Google Scholar]
15. Gülbağ S., Yılmaz Usta D., Gültekin H. E., et al. New perspective to develop memantine orally disintegrating tablet formulations: SeDeM expert system. *Pharmaceutical*

Development and Technology, 2018; 23(5): 512–519. doi:10.1080/10837450.2017.1345941. [PubMed] [CrossRef] [Google Scholar]

16. Sune Negre J. M., García Montoya E., Pérez Lozano P., et al. *Expert Systems for Human, Materials and Automation*. IntechOpen; 2011. SeDeM diagram: a new expert system for the formulation of drugs in solid form. Chapter 2 in: Vizureanu, Petrică, 17–34. [Google Scholar]
17. Chaudhary S. A., Chaudhary A. B., Mehta T. A. Excipients updates for orally disintegrating dosage forms. *International Journal of Research in Pharmaceutical Sciences*, 2010; 1(2): 103–107. [Google Scholar]
18. Gupta S., Saquib Hasnain M., Agarwal S. Formulation and evaluation of oral disintegrating tablets of itopride hydrochloride using ion exchange resins as drug carrier. *Asian Journal of Pharmaceutical Sciences*, 2012; 7(3). [Google Scholar]
19. Chowdary K., Suchitra B. Recent research on orodispersible tablets–a review. *International Research Journal of Pharmaceutical and Applied Sciences*, 2014; 4(1): 63–73. [Google Scholar]
20. Nagar P., Singh K., Chauhan I., et al. Orally disintegrating tablets: formulation, preparation techniques and evaluation. *Journal of Applied Pharmaceutical Science*, 2011; 1(4): 35–45. [Google Scholar]
21. Dhakane J. P., Kar A., Patel A. S., Khan I. Effect of soy proteins and emulsification-evaporation process on physical stability of lycopene emulsions. *International Journal of Chemical Studies*, 2017; 5(5): 1354–1358. [Google Scholar]
22. Liang A. C., Chen L.-L. H. Fast-dissolving intraoral drug delivery systems. *Expert Opinion on Therapeutic Patents*, 2001; 11(6): 981–986. doi: 10.1517/13543776.11.6.981. [CrossRef] [Google Scholar]
23. Gulsun T., Akdag Cayli Y., Izat N., Cetin M., Oner L., Sahin S. Development and evaluation of terbutaline sulfate orally disintegrating tablets by direct compression and freeze drying methods. *Journal of Drug Delivery Science and Technology*, 2018; 46: 251–258. doi: 10.1016/j.jddst.2018.05.014. [CrossRef] [Google Scholar] [Ref list]
24. Walsh J., Cram A., Woertz K., et al. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. *Advanced Drug Delivery Reviews*, 2014; 73: 14–33. doi: 10.1016/j.addr.2014.02.012. [PubMed] [CrossRef] [Google Scholar]
25. Patel P., Ahir K., Patel V., Manani L., Patel C. Drug-excipient compatibility studies: first step for dosage form development. *The Pharma Innovation*, 2015; 4(5, Part A) [Google Scholar] [Ref list]

26. Kumar R., Patil M. B., Patil S. R., Paschapur M. S. Development and characterization of melt-in-mouth tablets of haloperidol by sublimation technique. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2009; 1(1): 65–73. [Google Scholar]
27. Modi A., Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. *AAPS PharmSciTech*, 2006; 7(3): E87–E92. doi: 10.1208/pt070368. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Wang L., Zeng F., Zong L. Development of orally disintegrating tablets of perphenazine/hydroxypropyl-*β*-cyclodextrin inclusion complex. *Pharmaceutical Development and Technology*, 2013; 18(5): 1101–1110. doi: 10.3109/10837450.2012.700932. [PubMed] [CrossRef] [Google Scholar]
29. Debnath S., Yadav C. N., Nowjiya N., et al. A review on natural binders used in pharmacy. *Asian Journal of Pharmaceutical Research*. 2019;9(1):55–60. doi: 10.5958/2231-5691.2019.00009.1. [CrossRef] [Google Scholar]
30. Morkhade D. M. Comparative impact of different binder addition methods, binders and diluents on resulting granule and tablet attributes via high shear wet granulation. *Powder Technology*, 2017; 320: 114–124. doi: 10.1016/j.powtec.2017.07.038. [CrossRef] [Google Scholar]
31. Gryczke A., Schminke S., Maniruzzaman M., Beck J., Douroumis D. Development and evaluation of orally disintegrating tablets (ODTs) containing ibuprofen granules prepared by hot melt extrusion. *Colloids and Surfaces B: Biointerfaces*, 2011; 86(2): 275–284. doi: 10.1016/j.colsurfb.2011.04.007. [PubMed] [CrossRef] [Google Scholar]
32. Patil M. G., Kakade S. M., Pathade S. G. Formulation and evaluation of orally disintegrating tablet containing tramadol hydrochloride by mass extrusion technique. *Journal of Applied Pharmaceutical Science*, 2011; 1(6): 178. [Google Scholar]
33. Vehring R. Pharmaceutical particle engineering via spray drying. *Pharmaceutical Research*, 2008; 25(5): 999–1022. [PMC free article] [PubMed] [Google Scholar]
34. Badgujar B., Mundada A. The technologies used for developing orally disintegrating tablets: a review. *Acta Pharmaceutica*, 2011; 61(2): 117–139. doi: 10.2478/v10007-011-0020-8. [PubMed] [CrossRef] [Google Scholar]
35. Ghosh T., Ghosh A., Prasad D. A review on new generation orodispersible tablets and its future prospective. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2011; 3(1): 1–7. [Google Scholar]

36. Rameesa C., Drisya M. Orodispersible tablet: a patient friendly dosage form (a review) *Bali medical journal,* 2015; 4(1): 17–20. doi: 10.15562/bmj.v4i1.101. [CrossRef] [Google Scholar]
37. Omar S., AbdAlla F., Abdelgawad N. Effect of mannitol on physical characters of lyophilized fast-disintegrating tablets. *Journal of Advanced Pharmacy Research*, 2017; 1(4): 228–233. [Google Scholar]
38. Kasper J. C., Friess W. The freezing step in lyophilization: physico-chemical fundamentals, freezing methods and consequences on process performance and quality attributes of biopharmaceuticals. *European Journal of Pharmaceutics and Biopharmaceutics*, 2011; 78(2): 248–263. [PubMed] [Google Scholar]
39. Vanbillemont B., De Beer T. Application of polyvinyl acetate in an innovative formulation strategy for lyophilized orally disintegrating tablets. *International Journal of Pharmaceutics*, 2020; 588, article 119717 doi: 10.1016/j.ijpharm.2020.119717. [PubMed] [CrossRef] [Google Scholar]
40. Gulsun T., Akdag Cayli Y., Izat N., Cetin M., Oner L., Sahin S. Development and evaluation of terbutaline sulfate orally disintegrating tablets by direct compression and freeze drying methods. *Journal of Drug Delivery Science and Technology*, 2018; 46: 251–258. doi: 10.1016/j.jddst.2018.05.014. [CrossRef] [Google Scholar]
41. McLaughlin R., Banbury S., Crowley K. Orally Disintegrating Tablets. *Pharmaceutical Technology, Supplemental,* 2009; 78. [Google Scholar]
42. Stoltenberg I., Breitkreutz J. Orally disintegrating mini-tablets (ODMTs)–a novel solid oral dosage form for paediatric use. *European Journal of Pharmaceutics and Biopharmaceutics*, 2011; 78(3): 462–469. [PubMed] [Google Scholar]
43. Rameesa C., Drisya M. Orodispersible tablet: a patient friendly dosage form (a review) *Bali medical journal,* 2015; 4(1): 17–20. doi: 10.15562/bmj.v4i1.101. [CrossRef] [Google Scholar]
44. Vanbillemont B., Everaert H., De Beer T. New advances in the characterization of lyophilised orally disintegrating tablets. *International Journal of Pharmaceutics,* 2020; 579, article 119153 doi: 10.1016/j.ijpharm.2020.119153. [PubMed] [CrossRef] [Google Scholar]
45. Hannan P., Khan J. A., Khan A., Safiullah S. Oral dispersible system: a new approach in drug delivery system. *Indian Journal of Pharmaceutical Sciences,* 2016; 78(1): 2–7. doi: 10.4103/0250-474X.180244. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

46. Desai C., Prabhakar B. Development and evaluation of orally disintegrating tablets of cilostazol-*β*-cyclodextrin inclusion complexes. *Drug Development and Industrial Pharmacy*, 2015; 41(10): 1589–1607. [PubMed] [Google Scholar]
47. Shiino K., Oshima T., Sonoda R., Kimura S. I., Itai S., Iwao Y. Controlled-release fine particles prepared by melt adsorption for orally disintegrating tablets. *Chemical and Pharmaceutical Bulletin*, 2019; 67(10): 1152–1159. doi: 10.1248/cpb.c19-00554. [PubMed] [CrossRef] [Google Scholar]
48. Jacob S., Shirwaikar A., Nair A. Preparation and evaluation of fast-disintegrating effervescent tablets of glibenclamide. *Drug Development and Industrial Pharmacy*, 2009; 35(3): 321–328. [PubMed] [Google Scholar]
49. Patil M. G., Kakade S. M., Pathade S. G. Formulation and evaluation of orally disintegrating tablet containing tramadol hydrochloride by mass extrusion technique. *Journal of Applied Pharmaceutical Science*, 2011; 1(6): 178. [Google Scholar]
50. Desai C., Prabhakar B. Development and evaluation of orally disintegrating tablets of cilostazol-*β*-cyclodextrin inclusion complexes. *Drug Development and Industrial Pharmacy*, 2015; 41(10): 1589–1607. [PubMed] [Google Scholar]
51. Yu J., Shan X., Chen S., et al. Preparation and evaluation of novel multi-channel orally disintegrating tablets. *European Journal of Pharmaceutical Sciences*, 2020; 142, article 105108 doi: 10.1016/j.ejps.2019.105108. [PubMed] [CrossRef] [Google Scholar]
52. Chimombe T., Mukhopadhyay S., Veeroniaina H., et al. *Orally disintegrating tablets: formulation, preparation, Evaluation and Recent Advances, A.* 2019.
53. Elkhodairy K. A., Hassan M. A., Afifi S. A. Formulation and optimization of orodispersible tablets of flutamide. *Saudi Pharmaceutical Journal*, 2014; 22(1): 53–61. [PMC free article] [PubMed] [Google Scholar]
54. US Pharmacopeia. *<905> Uniformity of dosage units*. 2011. h.w.u. and org/sites/default/files/usp/document/harmonization/gen-method/q0304_stage_6_monograph_25_feb_2011.pdf.
55. Thulluru A., Palei N. N., Vimala M., Vidyasagar M., Vishnupriya K. Quality by design approach to optimize the taste masked zolpidem tartrate oral disintegrating tablets. *Research Journal of Pharmaceutical Dosage Forms and Technology*, 2018; 10(3): 139–148. doi: 10.5958/0975-4377.2018.00022.8. [CrossRef] [Google Scholar]
56. Ibrahim M. A., Abou el Ela A. E. S. F. Optimized furosemide taste masked orally disintegrating tablets. *Saudi Pharmaceutical Journal*, 2017; 25(7): 1055–1062.

doi: 10.1016/j.jsps.2017.04.002. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

57. Koner J. S., Rajabi-Siahboomi A. R., Missaghi S., et al. Conceptualisation, Development, Fabrication and _In Vivo_ Validation of a Novel Disintegration Tester for Orally Disintegrating Tablets. *Scientific Reports,* 2019; 9(1): 1–9. doi: 10.1038/s41598-019-48859-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
58. Thulluru A., Venkatesh K., Chowdhary E. T. S., Kakarla S. Formulation and evaluation of taste masked amlodipine besylate fast-dissolving sublingual tablets. *International Journal of Research and Development in Pharmacy & Life Sciences,* 2017; 6(6): 2824–2832. doi: 10.21276/IJRDPL.2278-0238.2017.6(6).2824-2832. [CrossRef] [Google Scholar]
59. Yadav D., Mishra A. Preparation and evaluation of orodispersible tablet of anti-inflammatory drug celecoxib. *International Journal of Recent Advances in Medical & Pharma Research,* 2018; 1(1) [Google Scholar]
60. Conseil de L'Europe. *European Pharmacopoeia,* 10: 323–324. [Google Scholar]
61. US Pharmacopeia. *<711>Dissolution.* 2011. h.w.u.o.s.d. and files/usp/document/ harmonization/genmethod/stage_6_monograph_25_feb_2011.
62. Abdelbary G., Eouani C., Prinderre P., Joachim J., Reynier J., Piccerelle P. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. *International Journal of Pharmaceutics,* 2005; 292(1-2): 29–41. doi: 10.1016/j.ijpharm.2004.08.019. [PubMed] [CrossRef] [Google Scholar]
63. El-Arini S. K., Clas S.-D. Evaluation of disintegration testing of different fast dissolving tablets using the texture analyzer. *Pharmaceutical Development and Technology,* 2002; 7(3): 361–371. [PubMed] [Google Scholar]
64. Fu Y., Yang S., Jeong S. H., Kimura S., Park K. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. *Critical Reviews in Therapeutic Drug Carrier Systems,* 2004; 21(6): 433–476. doi: 10.1615/CritRevTherDrugCarrierSyst.v21.i6.10. [PubMed] [CrossRef] [Google Scholar]
65. Thi T. H., Morel S., Ayouni F., Flament M. P. Development and evaluation of taste-masked drug for paediatric medicines–application to acetaminophen. *International Journal of Pharmaceutics,* 2012; 434(1-2): 235–242. [PubMed] [Google Scholar]
66. Madhavi B. R., Murthy V. S., Rani A. P., Kumar Y. M. Formulation and evaluation of taste masked oral disintegrating tablet of cefixime based on cyclodextrin binary

systems. *Journal of Global Trends in Pharmaceutical sciences*, 2014; 5(2): 1738–1746. [Google Scholar]

67. Alshehri S. M., Park J. B., Alsulays B. B., et al. Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology. *Journal of Drug Delivery Science and Technology*, 2015; 27: 18–27. doi: 10.1016/j.jddst.2015.03.003. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
68. Xu J., Bovet L. L., Zhao K. Taste masking microspheres for orally disintegrating tablets. *International Journal of Pharmaceutics*, 2008; 359(1-2): 63–69. [PubMed] [Google Scholar].