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ORODISPERSIBLE TABLETS – AN OVERVIEW

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Abstract: Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents. The tablet is the most widely utilized oral dose format. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is an orodispersible tablet (ODT). ODTs are the fast growing and highly accepted drug delivery system in now a day's mainly to improve patient compliance as it is readily dissolve or disintegrate in the mouth generally within <60 seconds without chewing and without water. The purpose of this article is to review the development of ODTs, novel technologies and novel excipients for formulation of ODTs, challenges in ODTs formulation, evaluation methods and future prospective.

Keywords: Orodispersible Tablets, Mouth Dissolving Tablets, Novel Excipients, Superdisintegrants, Patented Technologies.



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INTRODUCTION

The tablet is most popular solid dosage form. However one important drawback of these dosage forms for pediatric and geriatric patient is the difficulty to swallow. This difficulty in swallowing or dysphasia is currently affecting 37% of general population. Drinking water plays an important role in swallowing of oral dosage form. Often times people experience inconvenience in swallowing conventional dosage form such as when water is not available. To overcome this drawback, "orodispersible tablet (ODT)" has emerged as alternative oral dosage form [4, 5, 8]. The production of ODT technology entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding [15]. ODT are uncoated tablet intended to be placed in the mouth where they disperse rapidly before being swallowed. ODT are also known as "Mouth dissolving tablet," "Melt-in-mouth," "Fast dissolving drug delivery," "Rapimelt tablet," "porous tablet," "Quick dissolving tablet," etc. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia and Centre for Drug Evaluation & Research (CDER) [1]. According to US FDA defines in the "Orange Book" an ODT as "a solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of second, when placed upon the tongue [15]." According to European pharmacopoeia, ODT defines as "A tablet that is to be placed in mouth where it disperses rapidly within 3 minutes before swallowing [3]. The common reasons and clinical conditions in which ODT's are used are enlisted in table 1.

Ideal properties of ODT: [1, 7, 10]

- Drug and dosage form stability;
- Mechanical strength of final product;
- Taste, Mouth feel, Swallability;
- Rate of absorption from the saliva solution;
- Overall bioavailability;
- Allow high drug loading;
- Exhibit low sensitivity to environmental conditions such as humidity and temperature;
- Allows the manufacture of tablet using conventional processing and packaging equipment at low cost;
- Require no water for oral administration.

Advantages: [3, 7, 22, 28]

- Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patient, patients affected by renal failure and patient who refuse to swallow such as paediatric, geriatric and psychiatric patient.
- Rapid drug therapy intervention.
- Achieve increase bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, for traveller and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- Solid oral systems do not require sterile conditions, so less expensive.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.
- Accurate dosing as compared to liquids.
- Free risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.

Disadvantages: [3, 30]

- Hygroscopic in nature.
- Low amount of drug can be incorporated in each dose.
- Some time it passes with feeling.
- Highly fragile sometimes.
- ODT requires special packaging for properly stabilisation and safety of stable product.
- Eating and drinking may become restricted.
- Light sensitive drugs, ODT's may not be suitable as no option for film coating.

Formulation challenges and remedies for ODT as depicted in Table 2.

Selection of ODT drug candidates: ^[10, 15]

Suitable drug characteristic for ODT:

- No bitter taste.
- Dose lower than 20mg.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially non-ionized at the oral cavities pH.
- Ability to diffuse and partition into the epithelium of the upper GIT ($\log p > 1$, preferable >2).
- Ability to permeate oral mucosal tissue.

Unsuitable drug characteristic for ODT:

- Short- half and frequent dosing.
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- Required controlled or sustained release.
- Patient who concurrently take anticholinergic medication or with Sjögren's syndrome or dryness of the mouth due to decrease saliva production may not be good candidates for ODT.

Various novel excipients used in orodispersible tablet are described in table 3.

Conventional technology:

Freeze drying or lyophilisation: The process in which water is sublimated from the product after freezing. This technique is suitable for drying of heat sensitive drug and biological at low temperature (below -18°C) under condition that allow removal of water by sublimation. Lyophilisation results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improve absorption and bioavailability. Jaccard and Leyder used lyophilisation to create an oral pharmaceutical preparation that not only dissolve rapidly but also improve the bioavailability of several drugs such as, spironolactone and trolendomycin. Corveleyn and Remon studied various formulation and process parameter by using hydrochlorthiazide as a model drug one of which US patent 6,010,719 was granted ^[1, 24].

Freeze drying process normally consists of three steps:

- Material is frozen to bring it below the eutectic point.
- Primary drying to reduce the moisture around 4 % w/w of the dry product.
- Desorption or secondary drying to reduce the bound moisture up to required final volume.

Advantages: More rapid dissolution (< 5s) than other available solid products.

Disadvantages:

- High cost of equipments.
- Fragile and low mechanical strength which make them difficult to handle.
- Poor stability on storage under stressed conditions^[3].

Spray drying: It is a process by which highly porous, fine powders can be produced. Allen et al. have reported applying this process to the production of orodispersible tablets. The formulation that were produced contained hydrolyzed and unhydrolyzed gelatine as a support agent for the matrix, Mannitol as a bulking agent and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g. sodium bicarbonate). The tablet manufactured from this process, disintegrates in less than 20 seconds in an aqueous medium.

Advantages: Rapid disintegration of tablet.

Masareddy R et al studied the effect of co-processed excipient bases in formulation of microcrystalline cellulose with SSL-hydroxypropylcellulose was prepared using spray drier in 1:1, 1:2 and 1:3 ratio^[1, 3]. Maximum drug release and minimum disintegration time were observed with Kollidon CL excipient base compare to tablet prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique^[11].

Molding: Tablet prepared by this method are solid dispersion. The preparation of ODT using molding technology employs water-soluble ingredients so that the tablet disintegrates within 5-15 s and dissolves completely and rapidly. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Modi and Tayade prepared valdecoxib ODT using molding or solid dispersion. Laitinen et al studied the dissolution rate of perphenazine (PPZ), a poorly water soluble drug, by the solid dispersion technique using 0.1 mol L⁻¹HCl solution^[22, 24].

Different molding techniques:

- A) Compression molding
- B) Heat molding
- C) No vacuum lyophilisation

Advantages: In comparison to lyophilisation process, tablet produced by molding technique are easiest to adapt to the industrial scale.

Disadvantage: Poor mechanical strength may leads to the erosion and breaking during handling.

Sublimation: The key to rapid disintegration for orodispersible tablet is the presence of a porosity structure in the tablet matrix. Conventional compressed tablet that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe et al, Roser and Blair, inert solid that displayed high volatility (e.g. ammonium bicarbonate, ammonium carbonate benzoic acid, camphor, hexamethonium tetramine) were compressed along with other excipient into a tablet. The volatile material was then removed by sublimation and that result in formation of a porous matrix (approximately 30%) [1]. Suresh et al. prepared and evaluated salbutamol sulphate ODTs by using a volatile substance like camphor/ammonium bicarbonate and physicochemical properties of ODT evaluated were within the official limit and disintegration time was 5-40 s [24].

Direct compression: It is the easiest way to manufacture tablet. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in this method. This technique is now applied to the preparation of ODTs if good tablet disintegrates, Superdisintegrants, and sugar-based excipients are available. Disintegration of tablets prepared by direct compression depends upon the single or combines effect of disintegrant, water soluble excipient and effervescent agents. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases. Superdisintegrants a family of disintegrant that are superior to the traditional disintegrant in promoting the tablets to disintegrate in to their primary particles when place in an aqueous environment and are efficient at concentrations as low as 2-5% [1, 24].

Advantages:

- Simplest and cost effective.

- Requires fewer unit operations compared with wet granulation (shorter time and lower energy consumption)
- Fewer stability issues for drugs that are sensitive to heat or moisture.
- For certain drugs, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, norfloxacin.

Disadvantages:

- Issue with segregation these can be reduced by matching the particle size and density of the active drug substance with excipients.
- In general, drug content is limited to approximately 30% or approximately 50 mg.
- May not be applicable for materials possessing a low bulk density because after compression the tablets produced may be too thin.
- Not suited for poorly flowing drugs.
- Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing ^[19].

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

Advantages: Mask bitter taste by coating the granules.

Mansing G. Patil et al prepared orally disintegrating tablets of Trammadol hydrochloride for achievement of quick onset of action of the drug. An attempt was to prepare bitterless orally disintegrating tablet using Eudragit E 100 as a taste masking agent ^[3].

Melt granulation: Abdelbery et al describe a new approach for preparing ODTs whereby pharmaceutical powders are agglomerated by use of a binder that melts at a relatively low temperature. The binder is typically a hydrophilic wax like material such as Superpolystate[®], PEG-6-stearate which has a melting point of between 33 and 37°C. The material not only acts as a binder in the formulation but aids in the disintegration of the tablet as it will melt in the mouth at body temperature. The disintegration time of melt granulation tablets, however, was more than 1 min ^[18].

Advantages: No water or organic solvents are used in the process and therefore no drying of the granules is required and shorter production times.

Wet granulation: Bonadeo et al. described a process of producing ODTs by wet granulation in a fluidized bed. It was found that even with effervescent agents presented in the tablet with lower than 5%, quick disintegration times could be achieved. Furthermore, it was also found that fast disintegration time could be achieved using only the acid component of the effervescent couple. In the patent, the formulation includes poly alcohols (e.g., mannitol, xylitol, sorbitol, maltitol, erythritol, and lactitol), 1–30% of an edible acid, and an active ingredient as the dry mixture. This mixture was wet granulated with an aqueous solution of a water-soluble or water-dispersible polymer (e.g., poly (ethylene glycols), carrageenan, and ethylcellulose), which consisted of 1–10% of the final weight of the granule in a fluid bed. Granules with high porosity and low apparent density were obtained, and the tablets made by such granules had rapid disintegration times ranging from 3 to 30 seconds in the saliva. First, nanoparticles were formed by mechanical grinding, precipitation, or any other suitable sized reduction process. Those nanoparticles, less than 2 μm , were stabilized by surfactants. The particles were granulated with at least one pharmaceutically acceptable water-soluble or water dispersible excipient using a fluid bed, and the granules were made into tablets. The tablets had complete disintegration or dissolution in less than 3 minutes^[23].

Dry granulation: Eoga and Valia disclosed a method of making FDTs by dry granulation. Higher density alkali earth metal salts and water-soluble carbohydrates usually do not provide quick disintegration and a smooth mouth feel. Low-density alkali earth metal salts and water soluble carbohydrates are also difficult to compress and caused inadequate content uniformity. For these reasons, low density alkali earth metal salts or water-soluble carbohydrates were pre compacted, and the resulting granules were compressed into tablets that could dissolve fast. In this process, a powdered material with a density of 0.2-0.55 g/mL was pre compacted to increase the density to 0.4–0.75 g/mL by applying a force ranging from 1 to 9 kN /cm. The resulting granules were compressed into tablets^[23].

Phase transition process: In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. The combination of low melting point sugar alcohols (LMPSA) and high melting point sugar alcohols (HMPSA), as well as a phase transition in the manufacturing process, is important for making ODTs without any special apparatus. Here, tablet produced by compressing the powder containing two sugar alcohols of high and low melting point and subsequently heating at temperature between their two melting points. Kuno et al. have studied the effect of preparation method on the properties of orally disintegrating tablets manufactured using phase transition of sugar alcohol. Before heating process, tablet did not

have sufficient hardness because of low compatibility but after heating, increase in interparticular bonding or binding surface area occurs which then increased tablet hardness^[24].

Humidity treatment: The mechanical strength of some tablets increased substantially after moisture treatment, compared with the tablets before the treatment. The increase is known to be due to the formation of liquid bridges in the presence of moisture and then formation of solid bridges after drying. When an amorphous sugar is treated to go through the humidification and drying process, it changes to a crystalline state. This change increases the tablet strength substantially. In a patent by Mizumoto et al a drug, a sugar, and an amorphous sugar capable of transforming from amorphous to crystalline state were mixed and compressed into tablets. The "amorphous sugar" is those that can form an amorphous state by spray drying, freeze drying, or other granulation methods. The advantage of using amorphous sugar is that they have low critical relative humidity, so that they can absorb water even at low moisture levels. If a high humidity condition is used, tablets may adhere together, causing manufacturing problems^[18].

Sintering: When thermal energy is applied to a powder compact, the compact is densified and the average grain size increases. The basic phenomena occurring during this process, called sintering, are densification and grain growth. Lagoviyer et al disclosed a process that tablet strength can be increased by sintering the tablet components at high temperatures and then resolidifying them at lower temperatures. The disintegration time is generally within 3-60 seconds^[18].

Disintegrate addition: Disintegrate addition technique is one popular technique for formulating Fast-dissolving tablets because of its easy implementation and cost-effectiveness. The basic principle involved in formulating Fast-dissolving tablets by disintegrates addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel.

Orally disintegrating thin flim: It is a newer developing front in ODT that provides a very suitable means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, etc.) drug and other taste masking ingredients are dissolved in nonaqueous solvent to prepare non-aqueous solution, which forms a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. After placing this film in mouth, it melts or dissolves rapidly and releases the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 seconds with instant drug delivery and flavoured taste.

Patented technology: described in table 4.

Evaluation of ODTs: ^[12]

1) Measurement of tensile strength: The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using following equation:

$$T = 2F / \pi dt$$

Where, 'F' is the crushing load.

'd' denote the diameter.

't' is thickness of the tablet.

It is not applicable to very delicate tablets prepared by lyophilization technique and cotton candy process, because of poor mechanical strength. This test is best suited for tablets prepared by direct compression and moulding method.

2) Friability: The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for MDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is again not applicable for lyophilized and flashdose tablets, but is always recommended for tablets prepared by direct compression and moulding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

3) Moisture Uptake Study: The test can be carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37 °C for 24 hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the dessicator for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing. The materials with high moisture resistant properties should be used for packaging for e.g. alu strip pack, alu-alu blister or polyethylene sealing on blister. The use of appropriate quantity of desiccant in HDPE bottle packs with minimum head space is highly recommended to ensure stability of the product during its shelf life.

4) Measurement of Tablet Porosity: The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration. This instrument is based on the capillary rise phenomenon wherein an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure difference across the interface is given by the Washburn equation as follows, where the pressure drop is inversely related to the pore size (perpendicular radius).

$$\Delta P = - (2\gamma/r) \cos \theta$$

Where, γ is the surface tension of the liquid,

r is the perpendicular radius and

θ is the angle of contact between the liquid and the capillary walls.

Pore radius is calculated from equation using experimental data obtained in the form of P . In this test, the contact angle between mercury and the tablet is kept at 140° and the surface tension at the interface of mercury and the tablet is 0.486 N/m . Pore sizes in the range of $0.06\text{--}360 \mu\text{m}$, can be efficiently measured by this technique. Otherwise, the tablet porosity (ϵ) can also be calculated by using equation:

$$\epsilon = 1 - m / (\rho t V)$$

Where, ρt is the true density,

m is the weight and

V is volume of the tablet.

Tablets prepared by spray drying, lyophilization and cotton candy process generally possess high porosity and therefore, have extremely low disintegration time.

5) Wetting Time and Water Absorption Ratio: A study on wetting time and water absorption ratio reported the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R , was determined according to following equation:

$$R = 100 (W_a - W_b) / W_b$$

Where, W_b and W_a are the weights of tablet before and after water absorption, respectively.

6) Fineness of Dispersion: This is a qualitative test specified by EP for dispersible tablets. It is an assessment of the grittiness which arises due to disintegration of the tablet into coarse particles. The test is performed by placing two tablets in 100 ml water and stirring it gently, till the tablets get completely disintegrated. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μm without leaving any residue on the mesh.

7) Disintegration test: This type of test typically reveals unsatisfactory reproducibility and is not reliable as the difference in disintegration time is few seconds in most cases. In addition, the in-vivo disintegration test has its own limitation of issues related to ethics and the safety of the volunteers. At present, the disintegration time of MDTs is measured using the disintegration test for conventional tablets that is described in the Pharmacopoeias. EP has set the limit of 3 mins for disintegration time of MDTs using conventional disintegration apparatus. However, no special apparatus is mentioned in the pharmacopoeias for disintegration test of MDTs and the conventional method available seems to be inappropriate for MDTs. This is because of the extreme operating conditions in the disintegration apparatus which fails to provide a significant discrimination among the rapidly disintegrating tablets. Furthermore, the conventional test employs a relatively huge volume of test solution (900 ml) compared to the volume of saliva in human buccal cavity, which is less than 6 ml. Therefore, the results obtained from the conventional disintegration test do not reflect the actual disintegration rate in the human mouth which usually ranges from 5–30 secs. To overcome these issues, several new methods have been proposed, which are reviewed here shown in Table 5.

8) Dissolution Test: The conventional method of dissolution could be extended to in-vitro evaluation of MDT. The dissolution conditions for the reference listed drugs available in USP can be utilized for preliminary in-vitro studies to mimic better in-vivo conditions. Apart from the above, multimedia dissolution studies in various buffer solutions of different pH viz. 0.1 N HCl; pH 4.5 and 6.8 buffers should be carried out for interpretation of their in-vivo performance and pharmaceutical equivalence. USP apparatus II (paddle) with a speed of 50 rpm seems to be most suitable and common choice with appropriate dissolution media volume to maintain sink condition.

9) Evaluation of Effectiveness of Taste Masking:

In-vivo Method: The in-vivo taste evaluation consists of a double blind crossover study, carried out on a trained taste panel of healthy volunteers with sound organoleptic senses, with their prior consent. On placing the dosage form in the oral cavity, the disintegration time is noted after which it is further held in mouth for 60 sec by each volunteer, and the bitterness level is recorded against pure drug (control) using a numerical scale. After 60 sec, the disintegrated

tablet is spitted out and the mouth is rinsed thoroughly with mineral water. The numerical scale bears the following values: 0 = tasteless, 0.5 = aftertaste, 1.0 = slight, 1.5 = slight to moderate, 2.0 = moderate, 2.5 = moderate to strong, 3 = strong and 3+ = very strong. Along with the taste evaluation, a simultaneous observation of mouth feel (grittiness or smoothness) should also be noted to assess the quality of the product.

In-vitro method: The conventional in-vitro method of dissolution study lacks relevance to simulate the behavior of an MDT in the buccal cavity, due to excessively large dissolution media volume. Therefore, more relevant method was developed in our laboratory wherein 5 ml of pH 6.8 phosphate buffer (to simulate salivary pH and volume) was used to study the taste masking efficiency of risperidone resinate complex. The pharmaceutical taste assessment usually demands large panels and elaborate analysis, raises safety and scheduling issues, and can be time consuming and expensive. These challenges were overcome with the invention of a breakthrough electronic sensor array technology, the "E-tongue". This is a sensor device for recognition (identification, classification, and discrimination), quantitative multicomponent analysis and artificial assessment of taste and flavor. This unique device helps to considerably reduce the developmental time and costs, subjectivity, bias and safety concerns.

10) Weight variation ^[3]: 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 6.

11) Tablet thickness ^[22]: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

The different evaluation parameters of ODT's and their researchers mention in Table 7.

Regulatory ^[35]: The FDA has set regulations for filing a petition of a Supplemental NDA for a drug that has the same strength and route of administration as a drug listed in the FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," but differ in dosage form. This petition generally can be filed pursuant to section 505(b) (2) of the Federal Food, Drug and Cosmetic Act and 21 CFR x 314.93. Most of the ODT drug delivery systems fall under this category. Depending on the bioequivalence study, certain products can get approval under this clause or otherwise will need to establish safety and efficacy of the product by conducting further clinical trials. As ODT products do not require administration of water, it may be required to perform bioequivalence studies with and without water depending upon the nature of the drug. This will depend upon the difference of absorption of drug in the fed and fasted state and in addition may lead to a fed and fasted study.

Packaging ^[35]: Upon prototype selection, selection of a packaging configuration is a crucial part of an ODT dosage form. ODTs may require specialized packaging configurations owing to their relative high moisture sensitivity and fragility. In fact, the cost of packaging can be significant for commercialization. One approach used to overcome the moisture and physical issues with ODTs is to select a rigid, multilayer foil-based barrier material to protect the dosage form, with the blister actually forming during the tablet formulation process. In many cases, ODT are very fragile, and regular push through blister packaging may break the tablet upon removing from the blister, so the packaging requires a peelable closure. Blisterpackaged ODTs require specialized packaging equipment. In case of CIMA's PakSolv Technology, tablets are picked and placed in individual blister pockets "one at a time" using a robotic hand. In the case of freeze drying technology, each blister needs to be filled individually with the solution or suspension before subjecting it to freeze drying. The final packaged dosage form has to be evaluated to verify packaging integrity. One way to perform this is by immersing blisters in water and subjecting them to a vacuum for a specified period of time. The blisters are then opened manually and checked for presence of water droplets. Additionally, blisters and bottles should be monitored in simulated shipping tests according to American Society for Testing Materials (ASTM) standards. An additional issue with blister packaging is the evaluation of child resistance. The Consumer Product Safety Commission regulates this. The blisters are evaluated for "F" value, and appropriate designs need to be in place for child resistance and senior friendliness. The F requirement is determined from the toxicity of the drug. In the case of tablets, this would be the number of tablets that when ingested may produce a serious injury or serious illness based on a 25-pound child. A package passes a certain F rating, if 90% of the children from an initial 50-child test are not successful in accessing the required F number of tablets. As an example, if it is determined that an F $\frac{1}{4}$ 3 package is required and during testing with 50 children, 4 children are able to access three or more cells during the test, an F $\frac{1}{4}$ 3 rating is obtained at 92%. Commercializations of ODTs have to go through the final evaluation of long-term stability of the tablet matrix and packaging components per International Conference on Harmonisation guidelines. As the majority of ODT dosage forms on the market are sensitive to moisture, evaluation of moisture vapour transmission rate is an important parameter for assessing the shelf life of the product.

Conclusion: Future challenges for many ODT manufacturers include reducing costs by finding ways to manufacture with conventional equipment, using versatile packaging, and improving mechanical strength and taste-masking capabilities. ODT need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in travelling, patients who are may not have access to water. Such products provide opportunity for the product line extension in the market place and extension of patent term of innovator. Due to this wide significance of ODT, this drug delivery system may lead to

better patient compliance and ultimate clinical output. Future might witness many more classes of drugs developed in the form of ODT.

Table 1: Common reason and conditions for using ODT ^[1]

Medication type	Indication
Fast-acting	Pain, fever, heartburn, diarrhea, migraine, anxiety, insomnia
Compliance-critical	Parkinson's disease, Alzheimer disease, Schizophrenia, Hypertension, Cholesterol, Transplantation
Pediatric	Cough/cold/allergy, Pain, fever, ADHD

Table 2: Formulation challenges and Remedies [3, 15, 16, 35]:

Sr. no.	Parameters	Cause	Remedies
1.	Disintegration time and mechanical strength	Low compression force leads to fragile, soft tablet will break during packaging, transport or handling by patient.	Increase the mechanical strength will delay the disintegration time so, a good compromise is essential between these two parameter by proper adjustment of compression force.
2.	Taste masking	Bitter taste sensation of drug	Taste masking techniques like, formation of pellets, coating of drug by polymer, Drug- resinate formation, etc.
3.	Mouth feel	Larger particle may leads to unpleasant gritty mouth feeling	- To keep the majority of particle below the detectable size limit. - Addition of flavour to improve mouth feels perception.
4.	Excipients	Binder and melting characteristic of other excipients	- The binder and it's concentration is critical in ODT formulation - Melting characteristic of excipients should be around 30-35 ⁰ c for faster release.
5.	Environmental condition	- Low sensitivity to temperature and humidity. - Deliquescent substances.	A good packaging design to protect ODT from environmental conditions.
6.	Cost	Due to process, material, packaging and taste masking.	One step manufacturing process using conventional tableting technology.
7.	Size of tablet	Excess size of tablet may lead to the difficulty in swallowing and handling.	Easiest size to swallow: 7-8 mm Easiest size to handle: more than 8 mm. Use of multifunctional excipient.

Table 3: Novel Excipients [3, 18, 24]:

Sr. no.	Category	Example	Special comments
1.	Superdisintegrants	Kollidon®, Polyplasdone, Crosspovidone, etc.	Water insoluble and spongy in nature so get porous tablet.
2.	Bulking agent	Isomalt, Lactilol, Manitol, Sorbitol, Xylitol, Dextrose, Fructose, etc.	High aqueous solubility and sweetness, hence imparts taste masking properties and pleasing mouth feel.
3.	Binder	Starch, Gelatine, Polyvinylpyrrolidone, superpolystate® (PEG 6-stearate)	Used mostly in direct compression tableting
4.	Lubricants	Water insoluble: magnesium stearate, glyceryl behenate. Water soluble: polyethylene glycol, lauryl sulphate salt.	Concentration of lubricant is important consideration in ODT formulation, because it has a deleterious effect on tablet disintegration.
5.	Gliadant	Talc, Colloidal silicon dioxide	Improve flow property of the component of a powder blend, acting as moisture scavengers.
6.	Anti-adherent	Talc, Starch, Magnesium stearate	To reduce the adhesion between powder and punch surface
7.	Adsorbent	Kaolin, Bentonite or magnesium carbonate	Liquid/semisolid component bonded during a mixing process ensure that compaction is possible.
8.	Colourants	Water soluble dye, Water insoluble pigment.	Improve aesthetic appeal of ODT dosage form and for identification
9.	Flavourants	Orange, Strawberry, peppermint flavour, etc.	Produce more palatable dosage form.
10.	Cooling agent	Menthol	Improve the mouth feel.
11.	Sweeteners	Aspartame, Mannitol, etc.	Aspartame suitable for diabetic patient.

Table 4: Patented technology: [1, 6, 15, 18, 19, 23, 24, 25, 29, 34, 35]

Sr. no	Techniques/ Inventors	Specificity/ Novelty	Advantages	Disadvantages	Marketed Preparation
1.	Zydis (R. P. Scherer, Swindon, UK)	First to market, Freeze dried, Disintegrate in 10 seconds.	Quick dissolution, Self-preserving, increase bioavailability.	Expensive process, poor stability at higher temperature and humidities	Claritin Reditab (micronized loratidine 10mg), Feldene Melt (piroxicam 10 or 20 mg).
2.	Flash dose (Fuisz Technology Ltd).	Unique sinning mechanism to produce a floss-like crystalline structure, much like cotton candy, disintegrate within 1 min.	High surface area for dissolution	High temperature required to melt the matrix can limit the use of heat-sensitive to moisture and humidity, dosage can accommodate only up to 600 mg of drug.	Relivia Flash dose (Tramadol HCL).
3.	Wowtab (Yamanouchi Tokyo, Japan)	- Wow means "without water" - Combination of low-mouldability and high mouldability saccharides. -SMOOTHMELT action gives superior mouth feel, disintegrate	Adequate dissolution rate and hardness.	No significant change in bioavailability	Benadryl Allergy & Sinus Fastmelt (OTC), Children's Benadryl Allergy & Cold Fastmelt (OTC), GasterD (famotidine).

		in 15 seconds, particle size distribution 10-1000 micron.			
4.	Orasolv (Cima Labs, Eden Prairie, MN)	Unique taste masking, compressed, disintegrates in 60 seconds.	Taste-masking is two-fold, quick dissolution	Low mechanical strength	Remeron Soltab (mirtazepine 15, 30, or 45 mg).
5.	Durasolv (CIMA Labs).	Compressed dosage form, proprietary taste masking, disintegrate in 5-45 seconds.	Higher mechanical strength than Orasolv, good rigidity	Inappropriate with larger doses	NuLev (hyoscyamine sulphate 0.125 mg), Zomig ZMT.
6.	EFVDAS (Elan corporation)	Effervescent tablets, loosely compressed tablet, disintegrate in 60 seconds.	- Technique useful in development of number of OTC and prescription medication, i.e. particularly advantageous for conditions such as, cold, flu, etc. - Modified as, hot drink sachet products to produce pleasant-flavoured solution.	-	Ibuprofen, acetoaminophen, cimetidine, naproxen, and codeine and acetoaminophen combination product.
7.	Ziplets (Eurand,)	Incorporation of	Good	As soluble	Cibalgina

	Pessano con Bornago, Italy)	water-insoluble inorganic excipients for excellent physical performance	mechanical strength, handling problem during manufacturing are avoided, satisfactory properties can be obtained at high dose(450mg) and high weight(850mg), not required special packaging.	component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution	DueFast (Ibuprofen)
8.	Lyc (Framalyoc, France)	Freeze-dried wafer Blister packed Disintegrate in 10 seconds.	Lyc® tablets do not contain preservatives.	Low porosity that result in denser tablet.	Spansfon Lyc (Phloruglucinol hydrate)
9.	Nanocrystal or Nanomelt® (Elan, King of Prussia)	Lyophilised colloidal dispersion of drug substances and water soluble ingredient into blister pockets, Particle size less than 1000 nm.	Quick dissolution, avoid manufacturing process such as granulation, blending and tableting which is more advantageous for highly potent hazardous drugs.	Higher risk of toxicity due to large quantity of aerosolized powder.	-
10	Multiflash (Prographarm)	Multi-unit tablet composed of	Quickly disintegrates	Requires minimum	

		coated microgranules	in oesophagus.	amount of water for swallowing of tablet.	-	
11	Flashtab (Ethypharm (Paris, France))	Compressed dosage form containing drug as microcrystals, dissolve within 1 min.	Only conventional tableting technology is required.		-	Nurofen FlashTab (Ibuprofen).
12	Oraqquick (KV Pharmaceutical s)	MicroMask® taste masking.	Faster and efficient production, appropriate for heat-sensitive drugs		-	Hyoscyamine sulphate ODT
13	Pharmaburst (SPI Phrma)	- Coprocessed excipients to develop ODT - Dry blending of drug, flavour and lubricant followed dry compression into tablet and dissolve within 30-40 seconds.	Quick dissolution, Sufficient strength, so they can be packed in blister packs or bottle.		-	-
14	Shearform (Fuisz Technologies, Ltd).	Thin fiber matrix, loosely compressed tablet, disintegrates in 10 seconds.	The tablets are highly porous in nature and offer very pleasant mouth feel		-	In development
15	Ceform (Fuisz Technologies, Ltd)	Microspheres with very narrow particle size distribution.	Enhance solubility and stability, effective taste		-	-

			masking of drug.		
16	Frosta (Akina)	Plastic granules compressed at low pressure to produce strong tablet and disintegrate within 15-30 seconds.	Cost effective, high porosity and excellent hardness	-	-
17	Quick-Dis (Lavipharm)	Film produced by solvent casting method, disintegrate within 5-10 seconds and film thickness 2 mm. The typical release profile: 50% within 30 seconds and 95% within 1 minute.	Thin, flexible and Quick-dissolving film. Dispensed in various packaging configuration ranging from unit-dose pouches to multiple-dose blister packages.	-	-
18	AdvaTab (Eurand)	Microcap (microencapsulation) and Diffuscap CR technology disintegrate within 30 seconds.	suitable to patients that experience difficulty in swallowing capsules and tablet. Effective taste masking of drug.	-	AdvaTab cetirizine (cetirizine hydrochloride)
19	Quicksolv (Janssen)	Freeze dried tablet, blister packed, disintegrate in 10 seconds.	Uniform porosity and adequate strength for handling.	-	Propulsid Quicksolv® (cisapride)

20	Melt (Nutrition formulators)	Ease Dissolve within 5 sec (average 400 mg).	-	Cost effective. - Increase sales in two important markets, children and elderly for many nutritional supplements. - Sustained release on certain ingredient.	-	-
21	F-MELT® (Fuji chemical LTD.)	Co-spray dried powder. Available as: Type C (suitable for pharmaceuticals and nutraceuticals) and Type M (suitable for only pharmaceutical)	-	Cost saving, royalty free, user friendly and flexible excipient system for nutraceuticals and pharmaceutical industry.	-	Acetoaminophen, Aspirin, Vitamin C

Table 5: Type of disintegration test and researchers

Sr. no.	Type of disintegration test	Researchers
1.	Disintegration test using modified dissolution apparatus	Bi et al
2.	Disintegration test on wire cloth	Motohiro et al
3.	Disintegration test with CCD camera	Morita et al
4.	Disintegration test with rotary shaft method	Narazaki et al
5.	Disintegration test on shaking water bath	Fu et al

Table 6: Weight Variation Specification as per IP

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

Table 7: Evaluation parameter and researcher^[26]

Sr. No.	Evaluation parameter	Researcher
1.	Weight uniformity	D Bhowmik et al
2.	Hardness	Panigrahi R
3.	Frability test	Modasiya MK et al
4.	In- vitro drug release	Mahaveer Pr Khinchi
5.	Water absorption ratio	Mahaveer Pr Khinchi
6.	Disintegration time	Mahaveer Pr Khinchi
7.	Accelerated stability study	Mahaveer Pr Khinchi
8.	In-vitro dispersion time test	Shaikh S et al
9.	Wetting time	Shaikh S et al
10.	Thickness	Shaikh S et al
11.	Packaging	Kumari S et al

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