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Formulation And Evaluation Of Orodispersible Tablets:A Detailed Review

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I. INTRODUCTION

Oral route is presently regarded as the safest, most inexpensive and most convenient form of medication delivery resulting in high patient compliance. Oral administration of active ingredients comprises a range of technologies,many of which may be categorised as Orodispersible tablets(ODTs).Orodispersible tablets are also known as orally disintegrating tablets,mouth dissolving tablets, rapid-dissolving tablets,fast-disintegrating tablets,rapi-melts, fast-dissolving tablets[1].United States Pharmacopoeia (USP) approved these dosage forms as ODTs and recently the European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.The United States Food and Drug Administration (FDA) has defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue."The disintegration time of these ODTs usually ranges from several seconds to about a minute. Orally disintegrating tablets are advantageous for populations who have difficulty in swallowing. It has been stated that dysphagia (difficulty in swallowing) is common among all age groups and more specific with paediatric, geriatric population along with institutionalized patients and patients with complications like nausea, vomiting, and motion sickness. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups ofpopulation[2].Drug absorption and dissolution as well as onset of clinical effect and bioavailability of drug may be significantly greater than those seen in conventional dosage forms.When these ODTs are placed in oral cavity, salivaquickly penetrates into the pores causing quicker tablet disintegration.According to recent market research, more than half of patients favour ODTs to alternative dosage forms. Most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs over regular tablets or liquids (>80%)[3].

These tablets are currently available on the market for the treatment of a variety of diseases, including hypertension, migraine, dysphasia, nausea, vomiting, Parkinson's disease, schizophrenia, and paediatric emergency[2].

IDEAL PROPERTIES OF ODTS[3]:

- It dissolves, disperses, and disintegrates in the mouth in a matter of seconds without the use of water.
- Have a pleasant taste in the mouth.
- Have an acceptable taste masking property.
- Be harder and less friable
- No or leave minimal residue in mouth after administration.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Enable tablet production with standard processing and packaging equipment.

ADVANTAGES OF ODTs[4]:

- Administration of ODTs to the patients who have difficulty in swallowing, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as paediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.
- Rapid absorption and increased bioavailability is achieved through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and

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for travellers and busy people who do not always have easy access to water.

- Good mouth feel property helps to change the perception of medication as bitter pill particularly in paediatric patients.
- Avoidance of the risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

DISADVANTAGES[5]:

- Due to insufficient mechanical strength orodispersible tablets should be handled carefully
- Should be kept in a dry place as these ODTs are hygroscopic in nature.
- If not formulated accurately the tablets may leave disagreeable taste or grittiness in the mouth.
- Due to lack of physical resistance in standard blister packs, ODTs require special packaging for safety and stabilization of the product.
- ODTs have limited ability to incorporate higher concentrations of active drug.
- Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production and patients taking anticholinergic medications may not be good candidates for these tablet formulations.

NEED TO FORMULATE ORODISPERSIBLE TABLETS[3]:

Need for non- invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. ODT is a dosage form which is useful for Geriatric patients suffering from conditions like dysphasia and hand tremors.

•Paediatric patients who have trouble swallowing because their central nervous system and internal muscles have not fully matured.

• Traveling patients suffering from motion sickness and diarrhoea that do not have easy access to water.

• Mostly for Patients with persistent nausea for a long period of time are unable to swallow.

• Mentally challenged patients, bedridden patients and psychiatric patients.

CHALLENGES IN THE FORMULATION OF ORODISPERSIBLE TABLETS[4,5,6]:

1.Mechanical strength and disintegration time: ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile and there are many chances that such fragile tablet will break during transport, packing or handling by the patients.Tablets based on technologies like Zydis need special type of packaging. It is very logical that increasing the mechanical strength will delay the disintegration time.So, a good compromise between these two parameters is always essential.

2. Taste masking:Many medications have a bitter taste to them. A bitter medication tablet dissolving/ disintegrating in the mouth will have a significant impact on patient compliance and acceptance of the dosage form. As a result, excellent taste masking of bitter medications is required so that the drug's taste is not detected in the oral cavity.

3. Mouth feel:In the oral cavity, the ODTs should not breakdown into larger particles. The particles produced when the ODT disintegrates should be as tiny as feasible. After oral administration, ODT should leave little to no residue in the mouth. The addition of flavours and cooling substances such as menthol can aid improve mouth feel.

4.Sensitivity to environmental conditions: ODT generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in a ODT are meant to dissolve in minimum quantity of water.

5.Cost: The technology used for an ODT should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.

6.Amount of drug: The usage of technologies applied for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This factor is particularly challenging when formulating a fast-dissolving oral films or wafers.

7.Aqueous solubility: Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented

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by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

8. Size of tablet:The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

SELECTION OF ODT DRUG CANDIDATES[6] :

When choosing drug candidates for administration in ODT dosage forms, several considerations must be taken into account. An ODT is formulated as a bioequivalent line extension of an existing oral dosage form.Under this circumstance, it is assumed that the absorption of a drug molecule from the ODT occurs in the post gastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case.The pharmacokinetic characteristics of an ODT will differ depending on the degree of pregastric absorption. As a result, the ODT will not be bioequivalent to standard oral dosage forms. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form.

It is possible that these differences may, in part, be attributed to the drug substance, formulation, or mix of both. If significantly higher plasma levels have been observed, pregastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT. For example, safety profiles may be improved for drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pregastric GIT. Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2) and those able to permeate oral mucosal tissue are considered ideal for ODT formulations. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly,Patients with Sjogren's syndrome or dry mouth caused by low saliva production may also be unsuitable for these tablet formulations.Drugs with a short half-life and frequent dosing, drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved or those which require controlled or sustained release are unsuitable candidates of rapidly dissolving oral dosage forms. Researchers have developed ODTs for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction.

INGREDIENTS/EXCIPIENTS USED IN PREPARATION OF ODT[7]:

Important elements in ODT formulations should enable for rapid drug release, resulting in quicker dissolution. Both the active component and the excipients are included. The effects of disintegrants, water-soluble excipients, and effervescent agents on the disintegration and solubilization of a directly compressed tablet might be single or mixed.Excipients in ODTs help to balance the qualities of the active ingredients. To avoid interactions with the actives, a thorough understanding of the chemistry of these excipients is required.The choice of the binder is critical in a fast- dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used.

EXCIPIENTS/ INGREDIENTS	DESCRIPTION
Superdisintegrants	The inclusion of superdisintegrants accelerates the rate of disintegration and breakdown. They are more efficient in disintegrating and are effective at lowconcentrations.Examples:Crosspovidone,Microcrystalline Cellulose, Sodium Starch Glycolate, CMC.
Lubricants	Lubricants are used in reduction of the friction caused during

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	compaction and ejection of tablets. Examples: Magnesium stearate and Talc .
Binders	The selected binders should have proper melting characteristics, desired binding quality and produce quick release of active ingredients. Stability and integrity of tablets are maintained by proper selection of binders. Examples: Hydroxy propyl methyl cellulose, PVP, Polyvinyl alcohol.
Emulsifying Agents	These agents helps in enhancement of bioavailability and stabilizing the immiscible blends. By reducing the interfacial tension it improves the solubility of ODTs. Example: Sodium dodecyl sulphate.
Colour	Addition of colour will enhance appearance of dosage form. Examples:Amaranth3, Sunset Yellow, Redironoxide.
Flavours	Addition of flavours overcomes the undesirable taste and bitterness which improves acceptability and patient compliance. Examples: Citrus Oil, Vanilla, Clove Oil, Peppermint Oil.
Bulking Agents:	Addition of bulking agents will improve the textural characteristics of the drug which will increase the disintegration in the mouth. Examples: Mannitol and Starch hydrolysate.

SUPERDISINTEGRANT-THE IMPORTANT INGREDIENT IN ORODISPERSIBLE TABLETS[5]:

Disintegrating agents overcome the cohesive strength imparted during compression, thus aiding in the break-up of the tablet and increasing the surface area for dissolution.Several newer agents have been developed which are highly effective at lesser concentrations with greater disintegratingefficiency and mechanical strength. These agents are called 'Superdisintegrants'.Superdisintegrants when comes in contact with water they swell, hydrate, change volume or form and produce a disruptive change in the tablet.Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs.

METHODS OF INCORPORATING SUPERDISINTEGRANTS INTO TABLETS[12]

The following are the methods of incorporating disintegrating agents into the tablet:

- Intragranular(internal addition) - In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules.
- Extragranular(external addition) - In external addition method, the disintegrant is added to the dry granulation with mixing prior to compression.
- Partly intragranular and extragranular - In this method, part of the disintegrant is added internally and part externally. This results in immediate disruption of the tablet into granules while the disintegrating agent within the granules produces additional erosion of the granules into smaller particles

MECHANISM OF DISINTEGRATION OF TABLETS[8-11]:

1.Swelling:Swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

2.Porosity and Capillary Action (Wicking): Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture

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the interparticulate bonds causing the tablet to break apart.

3.Heat of wetting: When disintegrants with exothermic properties get wetted, localized stress is created due to capillary air expansion, which aids in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

4.Chemical reaction (Acid-Base reaction)**:** The tablet is quickly broken apart by internal liberation of CO2 in water due to interaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in presence of water. The tablet disintegrates due to generation of pressure within the tablet. Due to liberation in CO2 gas, the dissolution of active pharmaceutical ingredients in water as well as taste masking effect is enhanced. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during preparation of the tablets. The effervescent blend is either added immediately prior to compression or can be added in two separate fraction of formulation.

5.Deformation: Starch grains are generally thought to be "elastic" in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure.

6.By Enzymatic Reaction: Enzymes present in the body also act as disintegrants. These enzymes enhance the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration.

7.Due to disintegrating particle/particle repulsive forces: Another mechanism of disintegration attempts to explain the swelling of tablet made with "non-swellable" disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also causes disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. It was found by researchers that repulsion is secondary to wicking.

TYPE OF SUPERDISINTEGRANT AND THEIR EXAMPLE[13]:

1.Natural Superdisintegrants:These type of superdisintegrants are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and nontoxic in nature.

2.Synthetic Superdisintegrants: Synthetic super-disintegrants are frequently used in tablet formulations to improve the rate and extent of tablet disintegration thereby increasing the rate of drugdissolution.

3.Co-processed Blends[9]: New and improvedsuperdisintegrantscontinue to be developed to meet the needs of advanced tablet manufacturing. It requires the development of various added functionality excipients,which are used to achieve formulations with desired end effects. Upto until now only superdisintegrants areavailable to prepare the dosage forms, but recently different blend of excipients are available which canshow disintegration property. Some co-processedexcipients blends are designed to satisfy the need ofmore than one excipient.

Natural Superdisintegrants	Synthetic Superdisintegrants	Co-processed Blends[9]
❖ Plantago ovata Seed Mucilage (Isapgula) ❖ Mango Peel Pectin ❖ Hibiscus rosa-sinensis Linn. Mucilage ❖ Gum Karaya ❖ Lepidium sativum Mucilage ❖ Fenugreek Seed Mucilage ❖ Guar gum	❖ Cross-linked polyvinyl Pyrrolidone (Crosspovidone) ❖ Croscarmellose Sodium ❖ Sodium Starch Glycolate	❖ Ludiflash ❖ F-melt ❖ Pharmaburst ❖ Modified chitosan with silicon dioxide ❖ Mannogem EZ ❖ Pearlitol 200 SD ❖ Polacrilin Potassium ❖ Glucidex IT

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❖ Cassia fistula gum ❖ Locust Bean gum		

METHODS FOR PREPARING ORODISPERSIBLE TABLETS[14-21]:

1.Direct compression:

It is cost-effective and most easy manufacturing technique for ODTs. ODTs prepared by direct compression needs a standard equipment and a mixture of drug and excipients, especially the improved tablet excipients such as superdisintegrants and sugar-based excipients which lead to rapid tablets disintegration and enhanced dissolution. Hence, disintegration is considered a prerequisite for subsequent dissolution, which is an important step in preparing ODTs using this technology. Examples of superdisintegrantsinclude Crosscarmellose, Ac-Di-Sol, Crosspovidone, Sodium starch glycolate, Alginic acid, Satialgine, Soy polysacharrides, and Calcium silicate. Examples of sugar-based excipients include dextrose, maltose, fructose, mannitol, sorbitol and xylitol. Imparting sugar based excipients within an ODT formulation is useful due to being cost effective, having high aqueous solubility and sweet taste therefore, they are used for taste masking and producing a pleasant mouth feel.

2.Freeze-drying or Lyophilization:

In this method, the ODT formulation (the drug and the excipients) is firstly frozen below –18°C then,the pressure of the system is reduced giving the necessary heat that allows the sublimation process.In a water-soluble matrix the drug becomes physically entrapped which is then freeze-dried to provide a product that is highly porous and has a larger surface area. The increased porosity of the produced matrix increases its disintegration and subsequent dissolution. The main advantage of this technique is that it can be used for heat sensitive drugs thus, eliminating the adverse effect of high temperature on such APIs. The ideal drug candidate to be formulated by lyophilization is tasteless, water insoluble, with particle size smaller than 50 µm [9]. This technique is used in some patented technologies such as Zydis®, Lyoc®, and Quicksolv® technologies.

3.Tablet molding:

Molded tablets are solid dispersions. Since the dispersion matrix is made from sugars that are water soluble, they provide enhanced taste and rapid disintegration. Two methods are used to prepare ODTs using the molding technique namely compression molding and heat molding. Compression molding involves dampening the powder mixture, which is a blend of the drug and excipients, with a hydroalcoholic solvent followed by pressing into mold plates to form a wet mass. This step is then followed by air drying. The produced ODTs are less compact when compared to compressed tablets, having a porous structure which accelerates their dissolution. Also, molded tablets can be prepared by heat molding which involves dispersing or dissolving the drug in a molten matrix. In this method, agar solution is used as a binder. A suspension composed of the active constituent, agar and a kind of sugar such as lactose or mannitol is poured into a blister packaging, left to solidify at room temperature then, drying takes place under vacuum at 30ºC. Another method is called the “no-vacuum lyophilization” can be used. This method involves solvent evaporation from the drug solution or suspension at the standard pressure. Molded tablets acquire rapid disintegration because of the dispersion matrix and generally improved taste due to the involvement of water soluble sugars.

4.Sublimation:

The presence of a porous structure in the tablet matrix is the key stone to rapid disintegration for ODTs. In order to generate this porous matrix, volatile ingredients are used that are then subjected to sublimation. Examples of ingredients that are highly volatile include ammonium bicarbonate, ammonium carbonate, camphor, naphthalene, urea and urethane. These are called sublimating agents intended for forming a porous matrix. Also, some solvents such as benzene and cyclohexane are used to generate matrix porosity. Tablets manufactured by this method have been reported to disintegrate within ten to twenty seconds.

5.Mass extrusion:

This technique involves softening the drug-excipients blend using polyethylene glycol and methanol, followed by expulsion of this mass through an extruder or a syringe. An extrudate that is cylindrical in shape is produced which is then cut into uniform segments via a heated blade, forming tablets. An advantage of this method is being

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efficient in masking bitter taste of drugs through coating the granules.

6.Spray drying:

This method is broadly used pharmaceutical industry as it requires only a one-step process. Also, it can be easily controlled and can be easily scaled up. Thistechnique was used in preparation of microspheres where the particle size can bedetermined by the size of the nozzle of the spray dryer. Extremely porous and finepowders are obtained by this technique accordingly, it was used to prepare ODTs.Formulations of ODTs include a matrix forming agent such as gelatin, a bulking agent such as mannitol and a disintegrating agent such as croscarmellose sodium and sodium starch glycolate.Effervescent additives such as citric acid and sodium bicarbonate can be added to the formulations in order to enhance their dissolution and disintegration. ODTs produced via spray drying disintegrate in less than 30 seconds.

7.Cotton candy process:

Also known as the candy floss process. It is so named as it utilizes a uniquespinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. This process involves the formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT. This process can accommodate high doses of drug and offers improved mechanical strength. However, high process temperature limits the use of this process.

8.Melt granulation:

Melt granulation technique is a process by which pharmaceutical powders are proficiently agglomerated by a meltable binder. The merit of this technique when compared to conventional granulation is that no water or organic solvents are needed. For achieving this process, high shear mixers are utilized, where the product temperature is raised above the melting point of the binder by a heating jacket or by the heat of friction generated by impeller blades. This approach to prepare ODT with sufficient mechanical integrity involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33-37°C and aHLB value of 9. So it will not only act as a binder and increase thephysicalresistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilizes rapidly leaving no residues.

9.Phase transition:

A novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. 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 heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low/little compatibility.

10.Nanonization:

A recently developed Nano melt technology involves reduction in the particle size of drug to nano size by milling the drug using awet-milling technique.The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into ODTs.This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading toincreased absorption and hence higher bioavailability andreduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

11.Fast Dissolving Films:

In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropylmethylcellulose, hydroxyl ethyl cellulose,hydroxyl propyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol or sodium alginate, etc.)drug and other taste masking ingredients, which is allowed to form 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. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste.

12.Three-dimensional Printing (3DP):

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Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensionalprinting (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume.

EVALUATION PARAMETERS FOR ODT'S[22,23,24,25]

Ample techniques had been developed forODTs, but apartfrom European Pharmacopoeia (EP), nostandardizationtechniques had been described in other pharmacopoeias for evaluation of ODTs.

Thickness

It is a pertinent parameter in reproducing appearance andalso in counting by using filling equipment. The thicknessof ODTs is measured using vernier calliper.

Friability

It is significant challenge for manufacturer in order keep friability within 1% but atthe same time it shouldmeet the requirements of tablet mechanical strength and disintegration time limit. Like tablet tensile strength, the friability test is used for evaluating ODTs prepared using direct compression or molding but not for lyophilization and flash dose techniques.

Hardness/Crushing strength

The hardness of the tablet is measured by using conventional hardness testers like Monsanto/Pfizer hardness tester.A lower range limit of hardness helps in faster disintegration.

Wetting Time and Water Absorption Ratio

Indication of the inner structure of the tablets and thehydrophilicity of theexcipients is the wetting time.Thus, wetting time of a dosage form is related withthe contact angle. The lower the wetting time the faster is the disintegration of the tablets. The wetting time can be measured by using five circular tissue papers of 10cm in diameter, which are placed in a petridish of 10 cm diameter. Tenmillilitres of water-soluble dye like eosin solution is added to the petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time.For measuring water-absorption ratio, the weight of the tablet before keeping in the petridish is noted (Wb) and the wetted tablet from the petridish is taken and reweighted (Wa). The water-absorption ratio, R can be determined according to the following equation:

$R = 100 (Wa – Wb)/Wb.$

Weight Variation Test

This test is done as per Indian pharmacopoeia using20 tabletand electronic weighing balance.

In-vitro Disintegration test

The time taken for disintegration of ODTs is generally <1 min and actual disintegration time that patient can experience rangesfrom 5 to 30 s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not satisfy the measurement of very short disintegration times.The disintegration test for ODT shouldmimic disintegration in mouth with in salivarycontents. Following are the various in-vitro disintegrationmethods used for ODT's

Disintegration methods	Characteristic features	Critical parameters
Modified USP Apparatus II	One litre cylindrical vessel,Paddle as stirring element, basket sinker with ODT wasplaced in middle of vesseland hang by a hook tothe lid of vessel withdistance of 6-8.5 cm	Medium 900 ml, Temp 37°C, Paddle, 100 rpm
Rotary shaft method	Stainless steel wire gauzeon which ODT is placed andslightly immersed in medium. Rotary shaft is employed toprovide mechanical stress and rotation.	Rotational speed, Mechanical stress
Sieve	Glass cylinder with 10-meshsieve.	Medium 1 ml, Temp.

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method	Device is placed inshaking water bathoperated at 150 rpm.	37°C, Shaking speed of water bath
Texture analyzer	Cylindrical flat probe, thebottom of which is adheredby ODT, which was attached to load cell with very thin layerof glue. ODT submerged inmedium present in beakerorpetridish and compressed.Distance travelled by probeinto tablet is the measureofdisintegration time	Force of compression, medium 0.4 ml water.Room temperature, measures beginning and ending of disintegration time
Chargecoupleddevice method	Disintegration componentand measurement device, which involve continuousacquisition of picture by CCDcamera to recorddisintegration.Plastic cell divided in two partsone component inner tankcontaining stirring bar, second component is outertank of thermostated water.	Medium 200 ml, Temp. 37±2°C.

In-vitro Dispersion Time

In vitro dispersion time of prepared tablet was done by dropping the tablet in 10 ml measuring cylinder containing 6 ml of simulated salivary fluid/dissolution media.Time required for complete dispersion of tablet was measured.

In-vitro Dissolution test

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1 N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for ODT much in the same way as conventional tablets.

USP dissolution apparatus I and IIcan be used. USP I Basket apparatus may have certain applications, but sometimes tablet fragments or disintegrated tablet masses may becometrapped on the inside top of the basket at thespindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles.

USP IIPaddleapparatus, which was found to be the most suitable and common choice for ODTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of ODT is very quick when using USP monograph conditions, hence, slower paddle speeds may be utilized to obtain a profile.

The USPII Paddle apparatus at 50-100 rpm is suitable for dissolution testing of taste-masked drug as well. The media used for the taste-masked drug should match that of the finished product to maximize the value of the test. High-performance liquid chromatography (HPLC) is often required to analyse dissolution aliquots due to presence of UV absorbingcomponents, specifically flavours and sweetener. Excipient to drug ratio may be higher since the formulationis designed to have good taste and mouth feel, decreasing the detection of the drug to background (excipient) in the UV spectrophotometer.

PACKAGING OF ODT'S

The packaging is considered as the last step of tablet formulation and first step of marketing. The choice ofpackaging material for ODTs is imperative part frommanufacturers point. The packaging of ODTs should becarrying out in such way that it protects the physicalintegrity of ODTs and also it should create differentiationfrom other dosage form. The packaging is easiest waywhich creates product differentiation and patient's acceptance. The critical factors considered duringpackaging are the environmental conditions and hardnessof ODTs. The peelable closure is of choice for fragileODTs, but blister packing is also favoured. The packagingintegrity test should be performed for final dosage form.

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PATENTED TECHNOLOGIES

Technologies	Description
Zydis technology	Zydis® was introduced By R. P. Scherer Corporation in 1986. TheZydis process requires the active ingredient to be dissolved orsuspended in an aqueous solution of water-soluble structure forming additives then the mixture is poured into the preformed blisterpockets of a laminate film and freezedried. This results in a tablet shaped dosage form that spontaneouslydisintegrates in mouth in seconds. The two most commonly used structural additives are gelatin and mannitol although some other (e.g., starches, gums, etc.) may be used depending on the properties of the active ingredient. As a general rule, the best physical characteristics are achieved by using a mixture of a water-soluble polymer and a crystalline sugar alcohol or amino acid at a typical combined concentration of 10% w/w in the matrix solution. Thepolymer gives the strength and resilience while the crystalline component gives the hardness and texture.
Orasolv Technology	CIMA labs have developed Orasolv Technology.Active medicament is taste masked in this system. It also consists of effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to reduce oral dissolution time. Conventional blenders and tabletmachine is used to produce the tablets. The tablets produced are soft andfriable.
OraQuick	KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste maskingprocess does not utilize solvents of any kind, and therefore leads to quicker and more efficient production. Also, lower heat of production than alternative fast dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs.KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to obtain significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.
Wowtab Technology	The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. Wowtab technology is patented byYamanouchi Pharmaceutical Co.The WOW in Wowtab signifies the tablet is to be given “With Out Water”. It has just newly been introduced into the U.S. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol)excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide(good bindingproperty).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate.Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv.
Durasolv Technology	DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has increased mechanical strength than its predecessor

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	due to the use of higher compaction pressures during tableting. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity(friability less than that 2%). The DuraSolv product is thus produced in a faster and more cost-effective manner. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike OraSolv, thestructural integrity of any taste masking may be compromised with high drug doses.The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound.
Flash Dose Technology	Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development i.e., Flash Dose. The Flash Dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shear form. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly.
Flashtab Technology	Prographarmlaboratories has patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drugmicrogranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of micro-granules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets.All the processing utilized the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time lesser than a minute.
Ziplets/Advatab	This technology is patented by passano con Barnago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles.
Lyoc	Lyoc technology is patented by PHARMALYCO. O/W emulsion is prepared and placed directly into blister cavities followed by freeze-drying.During freeze-drying non homogeneity is avoided by incorporating inert filler to increase the viscosity finally the sedimentation is done.High proportion of filler reduces porosity of tablets due to which disintegration is lowered.
Pharmaburst	SPI Pharma, New Castle, patents this technology. It uses the co-

technology	processed excipients to develop ODT, which dissolves within 30-40 s. This technology involves dry blending of drug, flavour and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister and bottles.
Frosta technology	Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to obtain strong tablets with higher porosity. Plastic granules are composed of porous and plastic material, water penetration enhancer, and binder. The tablets obtained have excellent hardness and faster disintegration time ranging from 15 to 30 sec depending on size of tablet.
Nanocrystal Technology:	This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous drugs.

II. CONCLUSION:

The ODTs have received paramount popularity from quite some time now. There arenumerousdrugs that have been marketed as ODT formulation. The key feature of a ODTformulation is quick disintegration and dissolution in the mouth in presence of saliva. This can be attained by formulating a porous structure of the tablet matrix or by addition ofeffervescent agents and/or superdisintegrants. ODTsformulated by direct compression method usually possess good mechanical strength. This strength can be further improved by subsequent treatment, such as moisture treatment. ODTs provide a rapid onset of drug action enhancing bioavailability. Various clinical studies have shown that they can help inimprovement of patient compliance. However, future developments are required for costreduction and broadening the use of the new manufacturing techniques.

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