

Review Article

ORAL DISPERSED SYSTEMS FOR PHARMACEUTICAL PRODUCT DEVELOPMENT

Km. Shweta Mishra, Abadhesh Kumar Niranjana *

Department of pharmaceuticals, Hygia Institute of Pharmaceutical Education & Research, Lucknow, 226020, Uttar Pradesh, India

** Corresponding Author: Tel. No. : +91 8317008539, Email: niranjanpharma88@gmail.com*

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ABSTRACT

Last few decades have found oral disintegrating tablets (ODTs) as one of the most fascinating dosage forms and the pharmaceutical manufacturers have showed interest in its novel development approaches. These dosage form have exhibited potential activities and most importantly are more patient compliance as compared to other dosage forms. Usually, the ODTs when administered orally, they immediately disintegrate or dissolve to release the drug within shorter period of time, even in the absence of water. The ODTs are designed and developed based on its several advantages such as easy manufacturing and administering, no or minimal adverse effects, offers immediate drug release and increases the oral bioavailability. For patients like geriatric (old age), pediatric (children's), bedridden patients and for patients who traveling and not have access to water the oral disintegrating tablets formulated. For elderly or old age persons which have swallowing difficulty in taking tablets, capsules, suspensions and solutions like conventional oral dosage form because of hand tremors and dysphagia these oral disintegrating tablets formulations provide a product life extension opportunity. In this review we have summarized the major principle required for the development of ODTs, formulation challenges, drug candidate selection criteria, superdisintegrants used and their selection criteria. Apart from this, various conventional, patented approaches and evaluation procedures developed for ODTs that have gained significance in the international market and also various drug incorporated in ODTs have been discussed.

1. INTRODUCTION

In recent years, studies have showed that almost 50-60% of total drugs or dosage forms are administered through oral route. Out of solid dosage forms tablets and capsules are the most accepted solid dosage forms because of easy administration, accurate drug dosing, self-medication by patients and most considerably the patient compliance. Apart from these advantages of orally administered tablets or capsules, the major disadvantage is the difficulty to swallow a tablets and capsules. Also, the availability

of drinking water plays a crucial role in the intake of oral dosage forms. Sometimes people experience difficulty in swallowing conventional dosage forms such as tablet and capsules when for administration of tablets and capsules water is not available in the patients with motion sickness (kinetosis) and unexpected coughing episodes during the common cold, allergic condition and bronchitis. These oral disintegrating tablets without need of drinking water rapidly dissolve or disintegrate in the mouth or oral cavity widely accepted dosage form [1].

Recent advances in the novel drug administration system have been designed to prepare dosage forms to eliminate the various adverse effects, to offer immediate release and improve bioavailability. However, the oral medication administration system will be better. Tablets are an equally acceptable dosage form which provides a uniform dose and painless delivery. It is always the purpose of a designer or a scientist to formulate a dosage form & to increase the safety of user while to maintain its therapeutic efficacy and to develop such an oral disintegrating tablets. These novels are dosage forms that disintegrate in saliva at a specific time during tongue placement. This type of oral disintegrating tablet can be administered anywhere and anytime without the need for water, making it very suitable for children, the elderly, the disabled and patients with mental disabilities [2]. The availability of the oral delivery of protein and peptide-based active agents, improved therapeutic effect, improved safety like pharmaceutical and clinical advantages presenting by oral disintegrating tablets and commercial advantages including enlarged product diversity, extended patent life like commercial advantages and marketing advantages have attract awareness in the research and industrial fields [3].

The Center for Drug Evaluation and Research states an oral disintegrating tablet is a medicinal substance containing solid dosage form means oral disintegrating tablets which when placed upon the tongue disintegrate speedily usually within a matter of seconds [4]. Upon contact with the moist mucosal surfaces of the oral cavity these oral disintegrating tablets quickly release their components without water before swallowing. Oral disintegrating tablets disintegrate quickly in saliva within a few seconds without the necessity of taking water. So in comparison to conventional dosage forms dissolution or disintegration and absorption as well as onset of medicinal effect of drug can be obtained significantly quicker [5]. United States Food and Drug Administration defined an oral disintegrating tablets as a solid single unit dosage form containing active pharmaceutical agents or therapeutic agents which disperse within a time of few seconds when placed upon the tongue. [6] European Pharmacopoeia describe the oral disintegrating tablets when placed in the mouth or oral cavity so it disappears quickly before swallowing of tablet, stating a maximum disintegration time of 3 minutes [7].

1.1. Applications of ODTs

The need for ODTs persists because of patient's poor acceptance and patient's poor compliance with existing ways of drug delivery, narrow size of market for drug companies and uses of drug together with high cost of disease management. So, there is a need for oral disintegrating tablet like non-invasive drug delivery systems which overcome all these problems. [8-9] The number of important factors that are not fulfil by the conventional oral dosage forms then these factors are categorized into three groups which plays a most crucial and important role are as follows –

1.1.1. Patient related factors

ODTs are mainly fit for patients, who because of one or other reason find it difficult to swallow traditional tablets and capsules with a glass of water. These include the following:

- (a) Geriatric patients mainly suffering from conditions such as hand tremors and dysphasia (impaired ability to understand or use the spoken word) resulting in difficulty in swallowing.
- (b) Pediatric patients mean children's suffering from difficulty in swallowing of tablets and this swallowing condition known as dysphagia and because of their undeveloped internal muscles and central nervous system.
- (c) Patients during travelling suffering from motion sickness and diarrhea that do not have availability of water.
- (d) Patients which are suffering from long time constant nausea are unable to swallow a medicine.
- (e) Mentally challenged patients, bedridden (patients being too old or ill to get out of bed) and psychiatric patients also have swallowing problem.

1.1.2. Effectiveness factor

These are the factors related to therapeutic effect of drug which are not fulfil by conventional oral dosage forms due to this there is a need of ODTs are as follows – Increased bioavailability of drug and faster onset of therapeutic action are a major claim of these formulations.

- (a) Dispersion in saliva in the oral cavity or mouth causes pre-gastric absorption (by pass first pass metabolism of drug) from some formulations in those cases where the drug dissolves quickly and resulting in faster and maximum absorption of drug means increased bioavailability of drug and rapid onset of action at a site in body where the action is required.
- (b) For a drugs that undergo hepatic metabolism the first pass metabolism of drugs avoids by pre-gastric absorption of drugs can be of great advantage.

1.1.3 Manufacturing and marketing related factors

There is need of ODTs because of some manufacturing and marketing related factors are as follows –

- (a) All pharmaceutical manufacturers need to develop a given drug unit in a new and improved dosage form for better therapeutic effect when a present drug nears the end of its patient life.
- (b) A development of a new dosage form by a manufacturer provides many advantages to a manufacturer like to expand market superiority, unique differentiation of product, extension of value-added product line, and extend patent protection, while a more convenient dosage form offering to its patient population. This all-important factor leads to increased profits, while underserved and undertreated patient populations also targeting [10].

1.2. Biopharmaceutical considerations

When new drug delivery systems developed consider a biopharmaceutical factor like pharmacokinetic and pharmacodynamic factors.

1.2.1. Pharmacokinetics factors

- (a) Pharmacokinetic means absorption, distribution, metabolism and excretion taken into consideration. After absorption of drug the drug achieve the therapeutic level require for the therapeutic effect of drug so both rate and extent of absorption of drug is significant. In conventional dosage form there is delay in disintegration of time and as a result delay dissolution in existing conventional dosage form whereas in case of ODTs there is rapid disintegration in mouth or oral cavity and then the drug dissolution is rapid.
- (b) The number of factors like age, pH of gastrointestinal tract and flow of blood through gastrointestinal tract are taken into consideration because considered elder's patients or old age patients may be as separate distinctive Medicare population. The factors on which distribution of drug depends are permeability of tissue, perfusion rate, drug binding to tissue, state of disease, drug interaction etc.
- (c) In case of geriatric or old age patients, there is decreased volume of distribution of water-soluble drugs and increased volume of distribution of lipid soluble drugs because of decrease in body mass and total body water.
- (d) Duration and intensity of action depends upon metabolism of drug means conversion of active (lipid soluble) to inactive form (water soluble).
- (e) Biotransformation or metabolism of drug through oxidation, reduction and hydrolysis reduces because of decrease in liver volume, regional blood flow to liver. Excretion through a renal clearance is slowed so, renal excreted drugs half-life increase.

1.2.2. Pharmacodynamics factors

- (a) Due to undeveloped organ impaired in elderly or old age as well as in young adult drug reception interaction impaired.
- (b) In patients taking prazosin like antihypertensive there is decreased ability of the body to respond reflexive stimuli, orthostatic hypotension and cardiac output.
- (c) To b-adrenergic agonist and antagonist there is a decreased sensitivity of the cardiovascular system.
- (d) When antibiotics are administered the immunity is less and taken into concern.
- (e) When prescribed a multiple drug therapy the simultaneous illnesses present in elderly, also taken into consideration.
- (f) For various categories like cardiovascular agents, diuretics, anti-hypertensive in geriatrics the research workers have clinically evaluated drug combination. The choice of these drug combination choice depends on the patient disease state. [11]

1.3. Ideal requirements of ODTs

- (a) Have a pleasurable mouth feel.
- (b) No need of water in case of ODTs oral administration.
- (c) Have good property of taste masking.
- (d) Having less friable.
- (e) Show low sensitivity to temperature and mugginess like environmental conditions.
- (f) Minimal or no residue of formulation leave in the mouth or oral cavity after ODTs oral administration.
- (g) Low cost of manufacturing process because there is a manufacturing of tablets using processing and packaging conventional equipments [12].

1.4. Salient features of ODTs

- (a) Facilitate the administration of solid oral dosage form to patients who are not able to swallow the medicine for example Obstetric (children), geriatric (elderly person) and psychiatric (mental) patients.
- (b) ODTs exert rapid disintegration and absorption of drug, which shows fast onset of action.
- (c) ODTs are beneficial and improve acceptance for paralyzed patients and also beneficial for the patients who are traveling and not having instant access to water
- (d) There is no requirement of water to swallow the tablet and should dissolve or disintegrate in the oral cavity with the help of salivary juices within a matter of seconds.
- (e) After oral administration of tablets show minimum or no residue in the oral cavity.
- (f) Drug bioavailability is increased because some drugs from the mouth, pharynx and esophagus are absorbed as the saliva passes down into the stomach.
- (g) Due to pre-gastric absorption of drug the improved bio-availability and therapeutic effects of drug is achieved and reduce side effects because of reduce dosage of drug used.
- (h) In cases of insoluble and hydrophobic drugs a better bio-availability is achieved due to these ODTs rapid disintegration and dissolution [13-14].

1.5. Advantages of ODTs

- (a) Improved patient compliance is the main advantage of this dosage form.
- (b) Rapid onset of action as the tablet disintegrates within a matter of seconds.
- (c) Useful for patients like pediatric (childrens), geriatric (old age) and psychiatric patients who are unable or refuse to swallow and also appropriate when water is not available during traveling.
- (d) Give accurate dosing as in comparison to liquid dosage forms of same drug these ODTs give accurate dosing means exact dose of drug.

- (e) From mouth, pharynx & oesophagus as saliva passes down by pre-gastric absorption of drugs achieve improved bio-availability/rapid absorption of therapeutic agents [15].

1.6. Limitations of ODTs

- In case of formulation of oral disintegrating tablets difficult to formulate with relatively
- Large drug doses.
- For the patients who take anti-cholinergic therapeutic agents ODTs not be the finest candidates.
- Requires packaging and handling in carefully manner because of the reason that insufficient mechanical strength of tablet.
- If tablet is not formulated in proper manner the formulated tablets may leave unpleasant taste and/or grittiness in the oral cavity.
- These formulated ODTs are at more risk to degradation environment conditions like humidity and temperature [16].

1.7. Challenges of ODTs

- The Mechanical strength – To allow disintegration into the mouth or oral cavity porous or soft molded matrices used in formulation of ODTs. Its handling becomes difficult because this makes the tablet friable. Because of the use of higher compaction pressures during the compression pro-

cess. The Durasolv® has also a greatly higher mechanical strength than the Orasolv.

- The Palatability - Oral dispersible tablets are intended to be dissolved in mouth. There is a bitter taste of most of the drugs. Enough sweeteners and flavors to be included to mask the bitter taste by using a lipophilic vehicle, coating with polymers, carbohydrates, complexation of lipids or proteins with cyclodextrins or ion-exchange resins, salts formation and solid dispersions.
- The drugs used in the formulation of ODTs are hygroscopic in nature and due to this there is a need of protected from environmental condition like humidity. For counter this the humidity problem designed by simple methods a particular working facilities and set up a special air-conditioning systems. For ODTs the acceptable size of tablet is 7 and 8 mm and round shape punches having optimum dimensions make it easy to swallow while for proper handling purpose the size of tablets 8mm are easy to handle.
- There is a stability of drug candidates in both the water and saliva and these drug at oral cavity pH should not ionize and through oral mucosal tissue should be able to permeate to diffuse and partition in the upper gastro intestinal epithelium ($\log P > 1$, or preferably > 2 , not have short half-life).
- A special packaging is required for appropriate stabilization and safety of ODTs as a stable product [17].

Table 1: Classification of ODTs [18]

	1 st generation ODTs	2 nd generation ODTs	3 rd generation ODTs
Method	<ul style="list-style-type: none"> By using freeze-drying process 	<ul style="list-style-type: none"> By using graduation method. After compression of the wet mass dry the medication as well the excipients. 	<ul style="list-style-type: none"> By using dry granulation process. The drug agent and sugar containing dried mass were compressed.
Advantages	<ul style="list-style-type: none"> Fast ODTs dissociation 	<ul style="list-style-type: none"> Fast ODTs dissociation 	<ul style="list-style-type: none"> Fast dissociation of ODTs.
Disadvantages	<ul style="list-style-type: none"> Difficult Handling due to friable nature. Moisture sensitive. Low hardness and density. 	<ul style="list-style-type: none"> Low hardness. High porosity. Low density. 	<ul style="list-style-type: none"> High porosity. Low density. Low hardness.

1.8 Mechanism of action of ODTs

- By capillary action:** When the tablet is placed in a suitable medium by penetration The air adsorbed on the particles is replaced by the medium and thus they weaken the intermolecular spaces and bonds and then breaks the tablet into final particles.
- By heat of wetting:** Due to capillary air enlargement constrained stress is produced, when exothermic (exoergic or heat releasing) disintegrants gets moist which provides fast disintegration of the ODTs.

- By swelling action:** This is the maximal extensively trusted theory. Porosity (being able to absorb fluids) reveals a major function.
- By enzymatic reaction:** Through the homogenous (similar) enzymes in the body the binding property of the binders is reserved.
- Due to repulsive forces:** Non-swelling (shrinking) particles may also promotes ODTs disintegration as suggested by guyothermann in particle expulsion theory the mechanism of disintegration is the electric repulsive forces between the particles and water is required for it.

- **Due to release of gases:** The disintegration of tablets may occur due to the wetting of tablets and they release carbon dioxide gas when bicarbonate and carbonate of citric acid or tartaric acid gets interacted [19-20].

1.9. Drug selection criteria for ODTs

The following factors must be considered while selecting an appropriate drug candidate for development of orally fast disintegrating dosage forms:

- Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.
- Because due to a reason of taste masking cannot be achieved. Unsuitable for bitter or unacceptable taste Drugs
- Decreased saliva production in case of patients with dryness of the mouth or taking anticholinergic medications are unsuitable for formulations of ODTs.
- Acceptable Dose of drug in these ODTs is lesser than 20mg in quantity.
- Drugs with short half-life act as a suitable candidate for ODTs.
- The important criteria for selection of drug is they have notably different pharmacokinetic parameters as compared

with conventional dosage form containing the same dose of drug. Example- selegiline, apomorphine, buspirone etc.

- Drugs which have the 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 ODTs formulations [21-22].

1.10. Excipient selection criteria for ODTs

- It must be able to disintegrate quickly.
- On the ODTs final formulation properties the excipients properties not have any effect means compatible with drug and other excipients used in formulation.
- Doesn't interfere with the effectiveness and final product organoleptic properties.
- A care must be taken for selecting a binder (a single or combination of binders) to maintain the product final integrity and stability.
- The ideal and acceptable melting point range is between 30-35°C for the excipients used in the final formulation.
- The binder may be in liquid, semi solid, solid or polymeric in nature [23].

Table 2: Commonly used excipients for ODTs [24,25]

Excipients	Comment	Example	% w/w
Superdisintegrants	It increases the degree of dissolution and disintegration. For the fast and better effects of orally disintegrating tablet, the tablet must have rapid disintegrating property which is done by the help of super disintegrants.	Crosspovidone, MCC, Sodium starch glycolate, CMC, etc	1-15 %
Sweeteners	Sugar based additives behave as bulking agents. They reveal more aqueous solubility and sugariness and helps in taste masking.	Sugar derivative, Dextrose, Mannitol, Aspartame, Sorbitol, Maltose, Fructose.	0.5-1%
Binders	It maintains wholeness of dosage form	Examples – Polyvinyl pyrrolidone(PVP), Polyvinylalcohol(PVA), Hydroxypropyl methylcellulose(HPMC).	5-10 %
Surface Active agents	It reduces surface tension and hence improve dissolution of ODTs.	Examples – Sodium laurylsulfate, Sodium – doecylsulfate etc.	0.05% -15%
Lubricants	It helps in minimizing abrasion.	Examples–Stearic acid, Magnesium stearte, Zinc stearte, Talc, Polyethylene glycol.	0-10 %
Diluent	It enhances the bulkiness of solid dosage form.	Examples – Magnesium carbonate, Calcium carbonate, Mannitol, Sorbitol.	0-85 %
Colour	It improves appearance and physical properties of dosage form.	Examples–Sunset yellow, Red iron oxide, Amaranth 3.	0.5-1%
Flavors	It improves patient compliance.	Examples – Vanilla, Citrus oil, Fruit essence, Eucalyptus oil, Clove oil.	0.5-1%

2. SUPERDISINTEGRANTS SELECTION CRITERIA FOR ODTs

ODTs require faster disintegration. So, there is a need to formulate superdisintegrants which have greater disintegrating ability and are effective at low concentration with one disadvantage associated with these superdisintegrants is that they are hygroscopic and due to this disadvantage not used with drugs sensitive to moisture. These superdisintegrants act by mechanism of disintegration like swelling and in this swelling mechanism because of in the outer direction or radial direction exerted swelling pressure causes tablet to burst or the water accelerated absorption leading to promote disintegration by a huge increase in the volume of granules. The term disintegrants are defined as a substances or group of substances added as an important excipient to the formulations of tablets that make possible the tablets breakup or disintegration into smaller particles that more rapidly dissolve as compare to situation in which there is the absence of disintegrants. Tablet disintegration has been considered as the rate limiting step in faster drug release.

2.1 The ideal characteristics of superdisintegrants

- Poor solubility.
- Poor gel formation.
- Good hydration capacity.
- Good molding and flow properties
- No tendency to form complexes with the drugs.
- Doesn't show any incompatibility with the other excipients used in ODTs formulation and also have an advantageous tableting properties

2.2 Types of superdisintegrants used in ODTs

These superdisintegrants on the basis of their availability can be classified into two types:

- Natural Superdisintegrants:** Superdisintegrating of natural origin are preferred over synthetic origin based superdisintegrants because of some advantages of these natural superdisintegrants over synthetic superdisintegrants like cheaper, richly available, capable of multitude of chemical modifications, potentially degradable non-irritating and nontoxic in nature. In these natural superdisintegrants gums and mucilages have been extensively for drug delivery. Examples of natural superdisintegrants: Plantago ovata Seed Mucilage (Isapgula), Lepidium sativum mucilage, Gum karaya, Fanugreek Seed Mucilage, Guar gum, Cassia fistula gum, Hibiscus rosa-sinensis Linn Mucilage.
- Synthetic superdisintegrants:** A superdisintegrants like croscarmellose sodium sodium starch glycolate and crospovidone is a group of synthetic superdisintegrants used in formulation of these ODTs. Because of use of the superdisintegrants as a chief excipient in formulation of ODTs is possible as tablet shows optimum physical properties [28].

2.3. Conventional technologies for preparation of ODTs

(a) Freeze drying process or lyophilization method

Freeze drying process or lyophilisation method is the process in which water is sublimated from the product after freezing. This method is applied for drying of thermolabile (heat sensitive) drug.

Freeze drying process generally follows three steps:

- Below the eutectic point the material is frozen (chilled/iced).
- Primary drying to minimize the humidity approx 4 % w/w of the dry product.
- To reduce the bound moisture up to required final volume a secondary drying is used.

Advantages

- Fast disintegration (less than 5s) than other single unit dosage form.

Disadvantages

- Cost of equipments is high.
- Difficult in handling due to fragile nature and low mechanical strength.
- The stability is poor on storage under stressed conditions.

(b) Spray drying

A conventional technology Spray drying method used in preparation of oral disintegrating tablets by producing highly porous fine powders.

Advantages

- Disintegration of tablet is fast.

(c) Molding

Molding method is used in preparation of solid dispersion tablets. Water-miscible agents which can enhance disintegration of tablet within 5- 15 s and dissolves completely used in the preparation of ODTs. Through the mucosal lining of the oral cavity the active ingredients of the solid oral dosage form are absorbed. The different molding techniques used in preparation of ODTs are as follows:

- Compression molding
- Heat molding
- No vacuum lyophilization

Advantages

- ODTs produced by molding technique are easiest for taking to the industrial level.

Disadvantage

- The problems like erosion and breaking during handling may occur because of the poor mechanical strength.

(d) Sublimation

Presence of a porosity structure in the tablet matrix in this method used for formulation of ODTs is the main factor involved in the fast dissolution or disintegration. Because of low porosity of the matrix conventional compressed tablet contains highly

water miscible substances often fail to dissolve rapidly. Volatile ingredients are used for generating porous matrix later this is known as sublimation process.

(e) Direct compression

A direct compression method is the most common and easy way used in manufacturing of ODTs. If good tablet superdisintegrants and sugar-based excipients are available a direct compression is the most common technique for the preparation of ODTs. Concentration of disintegrants directly affects the tablet disintegration time. The time of tablet disintegration is inversely proportional to disintegrants concentration means disintegration time increases when concentration of disintegrants decreases or disintegration time decreases when concentration of disintegrants increases under critical concentration.

Advantages

- This is simple and cost-effective technique.
- Lower stability issues occur for thermolabile drugs.

Disadvantages

- This method is not suitable for the drugs that have poor flowing property.
- For the materials having low bulk density this process is not valid because the tablets produced by this method may be too thin after compression.

(f) Mass extrusion

Mass extrusion technology used in preparation of ODTs involves the active blend softening using the solvent mixture of water soluble polyethylene glycol and methanol and through the extruder or syringe expulsion of softened mass to get a cylindrical shaped extrude which are using heated blade to form tablets finally cut into even segments.

Advantages

- Coating of granules helps to mask bitter taste.

(g) Phase transition process

In phase transition process, ODTs are prepared by compressing and later heating tablets that consist of two sugar alcohols, one sugar alcohol with high melting point and other sugar alcohol with a low melting point.

Important steps involved in the preparation of ODTs-

- Low melting point sugar alcohols.
- High melting point sugar alcohols.
- Phase transition.

2.4. Patented technologies for preparation of ODTs

Rapid-disintegration feature of ODTs is generally certified to fast water penetration into tablet matrix resulting in its fast disintegration of ODTs. There are several technologies used other than the patented technologies in the ODTs preparation and several pharmaceutical companies patented these patented methods on the basis of formulation aspects and different processes.

(a) Zydis technology

In this technology within the fast dissolving carrier material matrix the drug or a medicinal agent is physically entrapped or dissolved. The ODTs produced by zydis formulation is a unique freeze-dried tablet that disintegrates immediately and does not require water for swallowing of tablets. There are a number of ingredients used in this zydis matrix to achieve a number of objectives such as polymers like gelatin, dextran or alginates. These polymers are used to provide properties like strength and resilience during handling.

Limitations

- For insoluble drugs the quantity of drug less than 60 mg and for insoluble drugs less than 400 mg is applicable in this technology.
- To prevent sedimentation during processing the particle size of the insoluble drugs should not be less than 50 μm and not more than 200 μm .

Advantages

- For the formulation like ODTs successfully prepared by this method area like buccal, pharyngeal and gastric regions are all areas of absorption of these ODTs.
- For the drugs that undergo a great deal of hepatic metabolism a pre-gastric absorption avoids first-pass metabolism.
- The ODTs formulated by zydis technology are self-preserving because in the freeze-dried product the final water concentration is too low to that allow for microbial growth.
- The tablets formulated by this patented technology allow patients compliance means for the patients who have swallowing difficulties.

Disadvantages

- Expensive manufacturing process.
- The formulation prepared by this patented technology is very light in weight and fragile in
- Nature and as a result not suitable for storage in backpacks or the bottom of purses.
- At higher temperatures and humidity like conditions these tablets have poor stability.

(b) Orasolv technology

CIMA labs developed orasolv technology in which the drug is taste masked and also an effervescent tablet disintegrating agent is used. Tablets are prepared by a technique called direct compression at low force of compression in order to reduce oral disintegration time of tablets. A conventional tablet manufacturing equipments such as blenders and tablet machine is used in formulation of tablets. A soft and friable tablets produced by using equipments like a conventional blenders and tableting machine and for the formulated tablets a specially designed pick and place system is used.

Advantages

- Taste-masking is two-fold,
- Rapid disintegration.

Disadvantages

- Must be packaged properly because the tablets prepared by this technology are moisture sensitive because of the existence of the effervescent system.
- These tablets have small mechanical strength.

(c) Durasolv technology

A patented method used in preparation of ODTs is Durasolv technology of CIMA labs. This tablets manufactured by this technology consist of a therapeutic agent, diluents and lubricant. Conventional tableting equipment used in preparation of tablets and these prepared tablets have good rigidity. Conventional form of packaging system like blisters packaging is used.

Advantages

- DuraSolv technology is mainly applicable for formulation of tablets consist of low amount in range of 125 mcg to 500 mg of active ingredients.
- A packaging flexibility is provided means the formulated tablets can be bottled and blistered.

Disadvantages

- With larger doses of active ingredients this patented technology is not well-suited because during compaction the formulation is subjected to high pressure.
- The bitter taste of drugs to the patient because during a process of compaction the drug powder coating may become fractured.

(d) Wow tab technology

Yamanouchi Pharmaceutical Co patented a technology called Wow (Without Water) tab technology for preparation of ODTs. In this method, a rapidly melting strong tablet is obtained by using a combination of low molding ability saccharides and high molding ability saccharides. Tablets of enough hardness is produced by a high and low molding ability combination.

Advantages

- Rapid dissolution or disintegration rate and hardness.
- Tablets manufactured by this method is packed in both into the conventional bottle and blister packs.

Disadvantages

- No major change in bioavailability of formulation.

(e) Pharmabust technology

SPI pharma patented this Pharmaburst technology. A dry blend of a drug, flavors, and lubricant is used in the patented technology and then followed by compression into tablets which within 30-40 seconds disintegrates. Sufficient strength is important property manufactured by this method and have can be packed in blister packs and bottles like packaging.

(f) Frosta technology

This type of patented technology is patented by Akina for formulation of ODTs. Plastic granules formulation involved and

then produce strong tablets by compression of granules. the key step in the process of this technology a mixing of the porous plastic material and water penetration enhancer and then next step is proper granulating with a binder [29-30].

2.5 Evaluation of ODTs

(a) Hardness/crushing strength

Hardness or crushing strength of ODTs is calculated by using a hardness tester called Monsanto hardness tester.

(b) Friability

Roche friabilator is used to measure friability of the punched tablets.

Normal range- 0.1% to 0.9%

(c) Wetting time

Wetting time is the sign of the inner structure of the ODTs and to the hydrophilicity (having a strong affinity for water) of the excipients. So, tablet wetting time is linked with the contact angle. Wetting time is inversely proportion to the disintegration of tablets:

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

Where,

R = water-absorption ratio

W_b = weight of tablet before keeping in the petridish

W_a = weight of wetted tablet

(d) Moisture-uptake studies

For ODTs moisture uptake studies is an important study. This study is done for the assessment of stability of the tablets. Ten tablets were kept for 24 hrs at 37° C in the desiccators over calcium chloride. Then these tablets were weighted and at room temperature for a duration of 14 days exposed to 75% relative humidity. At the bottom of the desiccators by keeping the sodium chloride saturated solution for 3 days the required humidity was achieved. Without superdisintegrants incorporation a one tablet was kept as control to evaluate the moisture uptake due to the presence of other excipients in the tablet. Then weigh the tablets for proper way to recorded the percentage increase in weight.

(e) Disintegration test

The in-vitro disintegration test to determine the in-vitro disintegration time by disintegration test apparatus. The ideal time of 1 minute as a disintegration time of ODTs.

(f) Dissolution test

Dissolution test by both the USP dissolution test apparatus paddle and basket type is used as an important test used for the determination of drug-release profile. Oral disintegrating tablets dissolution time is rapid means within a matter of seconds [31].

Table 3: Promising Drugs to be incorporated in ODTs [32]

Category	Drugs
Analgesics and Anti-inflammatory Agents	Indomethacin, Meclofenamic, Nabumetone, Aloxiprin, Etodolac, Fenbufen, Ibuprofen, Ketoprofen, Acid, Naproxen, Fenoprofen, Oxyphenbutazone, Piroxicam, Oxaprozin, Sulindac, Phenylbutazone.
Anthelmintics	Bephenium, Mebendazole, Albendazole, Oxarniquine, Dichlorophen, Oxfendazole, Thiabendazole.
Anti-arrhythmic Agents	Disopyramide, Quinidine Sulphate, Amiodarone, Flecainide Acetate
Anti-bacterial Agents	Ciprofloxacin, Doxycycline, Penicillin, Erythromycin, Ethionamide, Rifampicin, Sulphacetamide, Sulphafurazole, Sulphamethoxazole, Tetracycline, Clofazimine, Sulphabenzamide, Trimethoprim, Clarithromycin.
Anti-fungal Agents	Butoconazole Nitrate, Econazole Nitrate, Fluconazole, Griseofulvin, Ketoconazole, Clotrimazole, Miconazole, Natamycin, Terbinafine, Amphotericin, Terconazole, Tioconazole, Itraconazole.
Anti-depressants	Ciclazindol, Mianserin, Nortriptyline, Amoxapine, Trazodone.
Anti-epileptics	Carbamazepine, Clonazepam, Methoin, Methylphenobarbitone, Paramethadione, Phenobarbitone, Phenytoin, Valproic Acid.
Anti-coagulants	Dicoumarol, Nicoumalone, Phenindione.
Hypoglycemic Agents	Chlorpropamide, Gliclazide, Glibenclamide, Glipizide, Tolbutamide.
Anti-hypertensive Agents	Amlodipine, Carvedilol, Benidipine, Dilitazem, Phenoxybenzamine, Prazosin, Reserpine, Terazosin
Anti-Migraine Agents	Dihydroergotamine, Ergotamine, Sumatriptan

3. PATIENT COUNSELING POINTS FOR ODTs

- As pharmacist are ideal person to become familiar with recent technology advancement in novel dosage form, thus have opportunity to counsel the patient for effective treatment. Any confusion and misunderstanding regarding ODTs can avoid by educating the patients about ODTs.
- Pharmacist need to be clearly told about the difference between ODTs and effervescent tablets patients may mistake between ODTs and effervescent tablets. For example, the patients may experience a pleasant tingling effect on the tongue because cima technologies orosolv and durasolv use slight effervescence.
- Due to improper and insufficient mechanical strength these oral disintegrating tablet need to be handled carefully.
- These ODTs not appropriate for patients taking anticholinergic drugs or with dryness of mouth or with siogrens syndrome.

- The main advantage of ODTs is that there is no water is needed for administration of the drug and these oral disintegrating tablet utilizes own salivation but due to decreased saliva volume results in reduce dissolution/ disintegration/ bioavailability of the product.
- To reduce a confusion difference between chewable and ODTs. In a children's ODTs can be used who lost their primary teeth but do not have full use of their permanent teeth and also suitable for administration for patients who have lost their teeth permanently like geriatric (old age).
- With the pharmacist counselling, involvement and help all of these patients who taking ODTs for treatment of disease states could be treated more properly with greater ease. [33]

4. FUTURE PROSPECTS

These dosage forms may be suitable for the oral deliver these drugs, but the increased research into biopharmaceutics so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by ODTs, which may release these drugs in the oral cavity, are very promising for the delivery of high molecular weight protein and peptide. [34]

5. CONCLUSION

An innovative dosage forms for delivery of drugs ODTs are developed and specially designed to overcome problems and disadvantages like difficulty in swallowing in geriatric (old age) and pediatric (children's) patients associated with tablets, capsules like conventional solid dosage forms. These ODTs are developed to disintegrate or dissolve speedily in the saliva in the oral cavity within a time of less than 60 seconds (acceptable range of 5-60 seconds). The various advantages associated with ODTs drug delivery system are superior patient compliance and acceptance, improved biopharmaceutical means pharmacokinetic and pharmacodynamic properties, improved bioavailability results in improved therapeutic efficacy of medicinal agent. Over the last decade ODTs popularity has increased amazingly. For psychotic patients, bedridden, geriatric, pediatric patients, for those patients who are busy in traveling and for patients which have not easily availability to water there is a need of development of ODTs dosage forms. Conventional and patented technologies are used for development of these ODTs and these formulated tablets have adequate mechanical strength for proper handling, quick disintegration or dissolution in the oral cavity without need of water for swallowing of tablets. More successful ODTs dosage forms with more advantages and negligible disadvantages developed by utilizing these technologies.

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