



ORODISPERSIBLE TABLETS: AN OVERVIEW OF TECHNOLOGY

Vinita Chaurasia¹, Vikas Kumar², Brajesh K Tiwari³, Aakancha Jain⁴, Dharmendra Jain^{2*}

¹: Sagar Institute of Research and Technology Pharmacy, Bhopal (MP) 462041

²: Department of Pharmaceutical Sciences, Dr. H. S. Gour Central University, Sagar (MP) 470003

³: Sagar Institute of Pharmaceutical Sciences, Sagar (MP), 470002

⁴: Bhagyodya Tirth Pharmacy College Khurai Road, Sagar ((MP), 470003

* **Corresponding Author:** Department of Pharmaceutical Sciences, Dr. H. S. Gour University, Sagar (M. P.) 470003, Email: dharmjain@gmail.com

ABSTRACT

Tablet as the most common drug delivery system presents an opportunity for incorporation of novel technology for designing more advanced dosage form. Orodispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. The development of oral dispersible tablets (ODTs) has been done for pediatric, geriatric, bedridden and for those patients who may not have access to water. Basically swallowing problems also are happen in young individuals because of their under developed muscular and nervous systems. In some cases such as motion sickness, coughing, and unavailability of water, swallowing of conventional tablets may become difficult or improper. ODTs that dissolve or disintegrate rapidly in oral cavity result in solution, and presents an ultimate remedy for this problem. In addition they give pleasing mouth feeling. In formulation of ODTs, superdisintegrating agents are generally added to increase the drug release by achieving fast disintegration, and hence increases the bioavailability of drug. The aim of this article is to review the formulation of ODTs, analysing their advantages and limitations, challenges in formulation, use of new technologies, evaluation methodology, suitability of drug and excipients, patented technologies, marketed formulations and its future prospects.

Keywords: ODTs, Oral Route, Superdisintegrants, Tablet Technology, Patented Technology, Marketed Formulations.

1. INTRODUCTION

1.1 Orodispersible tablets

Oral route of drug delivery is most common and convenient for drug administration. The most popular solid oral dosage forms which have been used frequently are tablets and capsules [Nagar *et al.*, 2009]. Orodispersible tablets (ODTs) are oral solid dosage forms that disintegrate in the oral cavity within a minute without need of water [Sreenivas *et al.*, 2005]. They are also known as fast dissolving tablets, mouth dissolving tablets, quick dissolving tablets, melt-in-mouth, porous tablets, orally disintegrating tablets and rapimelts tablets [Ghosh *et al.*, 2011].

Orodispersible drug delivery systems were initially developed in the late 1970s as an alternative to capsules, syrups and tablets for geriatric and paediatric patients who were experiencing difficulties in swallowing traditional oral solid-dosage forms [Subramaniam *et al.*, 2013]. Orodispersible system is defined as a system that disintegrates and dissolves within seconds (or few minutes) when placed in mouth and water is not required for swallowing [Nagar *et al.*, 2009]. When the formulation comes in contact with saliva, it begins to disintegrate and complete disintegration occurs within 30-50 sec [Sisodiya *et al.*, 2013].

In order to improve the disintegration of tablets, superdisintegrants like Croscopovidone are usually added in the formulation. Agents like microcrystalline cellulose (MCC), sodium starch glycolate, crosscarmellose sodium, croscopovidone, are used in the formulations of orodispersible tablets [Selvi *et al.*, 2011].

The United States Food and Drug Administration defines a Orodispersible tablets [ODT] “a solid dosage form containing medicinal substance which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.” The disintegration time (Figure1) for ODTs normally ranges from several seconds to few minutes [Jeong *et al.*, 2008]. As compared to conventional dosage forms, ODTs bioavailability is normally greater [Sisodiya *et al.*, 2013].

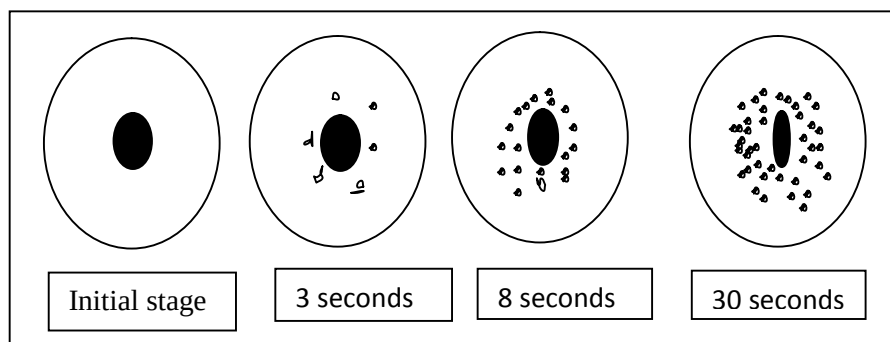


Figure 1: Images of dissolving ODTs at different time intervals

The formulations of ODTs are helpful to patients who experience swallowing difficulties. It is very useful for bedridden patients and travellers (usually not have ready access to water), and bedridden patients. ODTs are also useful for paediatric, geriatric and psychiatric patients and for the patients who used to avoid tablets and capsules due to fear of choking. As drug absorption is pregastric, so the dose of the drug can be reduced, thus a large amount of drug can be saved from hepatic metabolism. ODTs are stable for long time, as the drug is in solid dosage form till patient consumes it. It has combined advantages of both solid and liquid dosage form in terms of stability and bioavailability respectively. [Jeong *et al.*, 2008, Karpe *et al.*, 2012, Wagh *et al.*, 2010, Patil *et al.*, 2014, Soni *et al.*, 2011].

The disadvantages of ODTs includes unpleasant taste and/or grittiness may be left in mouth, if not formulated properly. The chances of degradation by humidity and temperature is comparatively more. Drugs which have larger doses are difficult to formulate as ODTs. Special packaging is required for proper stability and safety product. [Patil *et al.*, 2014, Asthana *et al.*, 2013, Nautiyal *et al.*, 2014]

The challenges involved in manufacturing of ODTs are that ODTs should possess enough strength to resist the difficulty of the manufacturing process and post-manufacturing handling. After administration, it should not leave residue in mouth. For administering conveniently, the tablet size should be easy to take and handle as well. Finally ODTs should disintegrate and dissolve in oral cavity without time delay. [Wagh *et al.*, 2010, Hirani *et al.*, 2009, Sharma *et al.*, 2011]

1.2 Drug selection criteria for orodispersible tablets formulation [Subramaniam *et al.*, 2013, Patil *et al.*, 2014, Velmurugan *et al.*, 2009, Khosla *et al.*, 2012]

There are several factors that should be considered while selecting an appropriate drug candidate in formulation of orally disintegrating tablets. For example, the drug should have the ability to permeate the oral mucosa with good solubility in water and saliva. Dose of the drug should be lower in ODTs (preferably less than 50 mg). It should be partially non-ionized at oral cavity pH. It should possess the ability to diffuse into the epithelium of the upper GIT. Drugs which need frequent dosing, have short half-life and possess bitter taste are unsuitable for formulation as ODTs. ODTs are also unsuitable in case of controlled/sustained release dosage form formulation. [Wagh *et al.*, 2010, Patil *et al.*, 2014]

1.3 Excipient selection criteria for orodispersible tablets [Nautiyal *et al.*, 2014, Krupa *et al.*, 2012]

Excipients (Table 1) which are used in orodispersible tablets contains at least one diluents i.e. Sorbitol, a superdisintegrant i.e Crospovidone, a lubricant i.e magnesium stearate, (optionally), a permeabilizing agent, a swelling agent, sweetening agent i.e sugar and flavouring agent i.e vanilla. Individual property of all excipients should not affect the stability of orodispersible tablets. Superdisintegrants produce mouth dissolving when tablet meets saliva in the mouth and also have enough compactability to produce less friable tablets [Rewar *et al.*, 2014]. Care must be taken in the selection of binders (single or combination of binders) so that stability remains unchanged. Types of excipients, examples and allowed percentage in formulation of ODTs are listed in table 1. Some marketed ODT's have been shown in table 2 with their drug therapeutic use and manufacturer.

Table 1: Types of excipients, examples and allowed percentage [Pandey *et al.*, 2012; Pandey and Dahiya 2016]

Excipients	Examples	% used
Superdisintegrants	Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Modified corn starch, Carboxy methyl cellulose etc.	1-15 %
Diluents	Magnesium tri silicate, Mannitol, Magnesium carbonate, Sorbitol, Calcium carbonate, Xylitol etc.	0-85 %
Binders	Polyvinyl pyrrolidone, Polyvinyl alcohol, Hydroxy propyl methylcellulose, etc.	5-10%
Antistatic agent	Sodium laury sulfate, sodium dodecyl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates etc.	0-10 %

Table 2: List of some orodispersible tablets present in market preparations [Subramaniam *et al.*, 2013; Jeong *et al.*, 2008; Yourong *et al.*, 2004; Debjit *et al.*, 2012, Sharma *et al.*, 2012; Pandey and Dahiya, 2016]

Name of drug	Therapeutic uses	Brand name	Manufacturer
Acyclovir	Antiviral Agent	Acivir DT	Cipla
Cefixime	Anti-Bacterial Agents	Cefinar DT	Zydus Alidac
Mirtazapine	Antidepressant	Remeron SolTab	Organon
Diphenhydramine pseudoephedrine	Allergy, cold, sinus	Benadryl Fast	Johnson and Johnson
Piroxicam	NSAIDs	Feldene Fast Melt	Pfizer, NY, USA
Piroxicam	NSAIDs	Ugesic	Mayer organic Ltd.
Ondansetron	Anti-emetic	Zofran ODT	Glaxo Wellcome, Middlesex, UK
Ondansetron	Anti-emetic	Zofer MD	Sun Pharma
Ondansetron	Anti-emetic	Ondem MD	Alkem Pharma

Nimesulide	NSAIDs	Esulide MD	Doff Biotech
Nimesulide	NSAIDs	Kazoldil MD	Kaizen Drugs
Mosapride	Migraine Treatment	Mosid MD	Torrent Pharma
Valdecoxib	NSAIDs	Valus	Glenmark
Domperidone	Anti-emetic	Vomidon MD	Olcare lab
Loratidine	Antiallergic	Claritin redi Tab	Schering Plough Corp., USA
Loratadine	Antiallergic	Alavert	Wyeth
Rizatriptan	Migraine Treatment	Maxalt MLT	Merck and Co., NJ, USA
Olanzapine	Antipsychotic	Zyprexa	Eli Lilly., Indianapolis, USA
Famotidine	Antiulcer	Pepcid RPD	Merck and Co., NJ, USA
Zolmitriptan	Migraine Treatment	Zoming-ZMT	AstraZeneca, USA
Selegiline	Anti-Parkinsonism	Zeplar TM	Amarin Corp. London
Acetaminophen	NSAIDs	Tempra Quiclets	Bristol Myers Squibb. USA
Paracetamol	NSAIDs	Febrectol	Prographarm. France
Nimesulide	NSAIDs	Nimulid MDT	Panacea Biotech. India
Rofecoxib	NSAIDs	Torrox MT	Torrent Pharmaceuticals, India
Rofecoxib	NSAIDs	Rofixx MD	Cipla ltd. Mumbai India
Olanzapine	Antipsychotic	Olanex Instab	Ranbaxy Lab. Ltd, India
Monteleukast	Antiasthmatic	Romilast	Ranbaxy Lab. Ltd, India
Cetirizine	Antiallergic	Zontec MD	Zosta Pharma India
Olanzapine	Antipsychotic	Lonazep MD	Sun Pharma
Nimesulide	NSAIDs	Nime MD	Maiden Pharma
Loperamide	Anti-Diarroheal	Imodium lingual	R.P. Scherer Corp., U.S.A
Famotidine	Antiulcer	Pepcidin Rapitab	Merck & Co., U.S.A

Ibuprofen	NSAIDs	Cibalginadue Fast	Novartis Consumer Health
Ibuprofen	NSAIDs	Nurofen Flashtab	Booth healthcare
Hyoscyamine sulfate	Antispasmodic	Hyoscyamine sulphate ODT	Ethex Corporation
Risperidone	Antiemetic	Risperdal M Tab	Janssen
Lopermide HCl	Anti-Diarrhoeal	Imodium Instant Melts	Janssen
Cisapride monohydrate	Treatment of GERD	Propulsid Quick Sol	Janssen
Loratadine	Antiallergic	Alavert	Wyeth Consumer Healthcare
Hyoscyamine sulfate	Antispasmodic	NuLev	Schwarz Pharma
Baclofen	Antidepressant	Kemstro	Schwarz Pharma
Ramosetron HCl	Antiemetic	Nasea OD	Yamanouchi
Famotidine	Antiulcer	Gaster D	Yamanouchi
Fluoxetine	Antidepressant	Fluoxetine ODT	Biovail
Zolpidem tartrate	Treatment of Insomnia	Zolpidem ODT	Biovail
Acetaminophen	NSAIDs	Excedrin Quick Tabs	Bristol-Myers Squibb
Aripiprazole	Antipsychotic	Abilify Discmelt	Otsuka America
Donepezil	In Alzheimer disease	Aricept ODT	Eisai Co.
Clozapine	Antipsychotic	FazaClo	Azur Pharma
Tramadol HCl	for chronic pain	Relivia Flash dose	Fuisz Technology, Ltd
Domperidone	Antiemetic	Domray MD	Ray Remedies

2. Factor considered for the development of orodispersible tablets [Patil *et al.*, 2014, Nautiyal *et al.*, 2014, Hirani *et al.*, 2009, Khosla *et al.*, 2012, Sharma *et al.*, 2012]

Patient related factors, effectiveness factors, manufacturing and marketing factors are usually needed to be considered for the development of ODTs. Here it is necessary that above all the factors should be studied and analysed carefully for the effective development of an ODT.

The patient related factors includes geriatric and paediatric patients who have difficulty in the administration of solid dosage forms. In case of travelling where patient do not have easy access of water or suffering from motion sickness or diarrhoea.

Effectiveness factors are responsible for the better therapeutic efficacy as well as bioavailability. ODTs shows pre-gastric drug absorption which avoids the first-pass metabolism,

thus loss of extensive amount of drug may be reduced during hepatic metabolism. Faster onset of action and increased bioavailability are main demands from these formulations.

For the development of improved drug entity the manufacturing and marketing factors are usually very useful for pharmaceutical manufacturer. When manufacturer presents an easier way to make a formulation and they can build an improved brand and company image. Manufacturer extends their market exclusivity by formulating new dosage formulations, which should follow the biopharmaceutical parameters: [Ghosh *et al.*, 2011, Divate *et al.*, 2011]

2.1 Pharmacokinetics: Drug achieves therapeutic level after absorption which increases pharmacologic effect. Pharmacologic response usually delays when drug shows delay in disintegration and dissolution. But in case of ODTs this delay is avoided as drug disintegrates and dissolves rapidly in oral cavity. Drug absorption starts from mouth, pharynx and oesophagus. Distribution factors includes binding of drug to tissue, tissue permeability, drug interaction, disease state, etc. Biotransformation (metabolism) refers to as the rate of removal of drug from site of action or body, and intensity, duration of drug action depends on biotransformation. Metabolism of drug is generally reduced due to decrease in liver blood flow. Half life of drugs is increased by slow renal clearance. [Ghosh *et al.*, 2011].

2.2 Pharmacodynamics: Due to inappropriate development of organs in elderly and some adults, there is impairment of drug receptor interaction.

3. Challenges in formulation of orodispersible tablets

Following are some of the challenges involved in formulation of orodispersible tablets:

3.1 Mechanical strength and disintegration time: Mechanical strength of the tablets should be maintained, as it is accepted that on increasing the mechanical strength, disintegration time is delayed. To allow good disintegration in oral cavity, ODTs should be made with very low compression force [Krupa *et al.*, 2012, Asthana *et al.*, 2013].

3.2 Taste masking: In case of unpalatable drugs, taste masked form of medicament for rapid drug delivery is preferred. Drug delivery system releases active ingredients by disintegrating or dissolving in the oral cavity. Hence, taste masking is very critical step to provide patient compliance [Nautiyal *et al.*, 2014, Khosla *et al.*, 2012].

3.3 Aqueous solubility: Water soluble drugs forms eutectic mixtures, so they form glassy solid which may break on drying due to lack of supporting structure during sublimation method, so this presents various formulation challenges for manufacturers [Asthana *et al.*, 2013, Sharma *et al.*, 2012].

3.4 Mouth feel: ODTs should be disintegrated into smaller fragments in the patient's oral cavity. For patient's palatability, generated fragments should not be large as well as the taste of drug should not be too bitter [Panchal *et al.*, 2013, Sharma *et al.*, 2012].

3.5 Hygroscopicity: Orodispersible tablets should have less sensitivity to humidity. This might be challenging task for manufacturer as various hydrophilic excipients are added in the formulation in order to get faster dissolution. Hence, ODTs usually need higher protection from humidity [Krupa *et al.*, 2012, Khosla *et al.*, 2012].

3.6 Amount of drug: Amount of drug that has to be incorporated in each unit dose can be a limitation factor for development of ODTs. Quantity of drug in lyophilization technology should be less than 400mg and 60mg for insoluble drugs and soluble drugs respectively [Sharma *et al.*, 2012, Panchal *et al.*, 2013].

3.7 Size of tablet: Tablet size should be selected by considering its ingestion as well as handling. Reported size of tablet to swallow is 7-8 mm, but for handling purpose it should be larger than 8 mm. So, the tablet size which is easy to take and handle is difficult to achieve [Sharma *et al.*, 2012, Asthana *et al.*, 2013].

3.8 Environmental conditions: ODTs are meant to dissolve in minimum quantity of water, so many excipients are added which may be sensitive to environmental condition such as temperature and humidity [Sharma *et al.*, 2012, Khosla *et al.*, 2012].

4. Orodispersible tablets drug release technology [Asthana *et al.*, 2013, Kaur *et al.*, 2011, Zhao *et al.*, 2005, Yadav *et al.*, 2011]

Orodispersible technology works with the help of *superdisintegrants* (Table 3 and Figure 2) when it comes in contact with surrounding medium. Mechanisms for the disintegrants action include water uptake through swelling, wicking, deformation (shape) recovery, heat of wetting and particle repulsion. Examples of superdisintegrants are Sodium Starch Glycolate, Crospovidone, Ac-di-sol etc. There are some factors which can affect the drug release pattern from the ODTs.

Table 3: Some superdisintegrants and their mode of action [Debjit *et al.*, 2009, Chotaliya and chakraborty, 2012]

Superdisintegrants	Mechanism of Action
Crosscarmellose Ac-Di-Sol (e.g. Cross linked cellulose)	Swelling and wicking action
Crospovidone (e.g. Crosslinked PVP)	Capillary action
Sodium starch glycolate Explotab (e.g. Crosslinked Starch)	Swelling action Swells 7-12 folds in less than 30 seconds
Alginic acid (e.g. sodium alginate) Calcium silicate	Wicking action

4.1 Factors affecting drug release from ODTs

Following are some of the factors which affect the release of drug from the orodispersible tablets:

4.1.1 Swelling index: It is a test by which swelling efficiency of superdisintegrants are measured. It denotes the volume occupied by 1 gm of drug or any adhering mucilage after swollen in aqueous medium [Yadav *et al.*, 2011].

4.1.2 Deformation: Disintegrated particles get deformed during compression of tablet but regain their initial shape when comes in contact with aqueous media. So, the disintegrant particle regains their precompression size and disintegration of tablet is resulted [Asthana *et al.*, 2013]. It usually occurs due to following action as presented in figure 2 and 3.

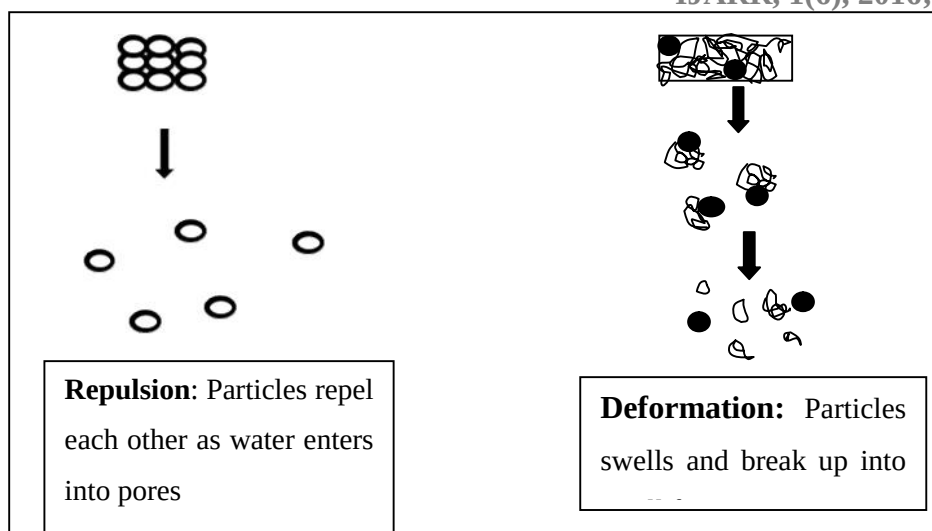


Figure 2: Image of disintegration phenomenon [Adapted from Rao *et al.*, 2012]

4.1.3 Particle repulsive forces: Particle repulsion theory is proposed by Guyot- Hermann, which is based on the observation that non swelling particle also cause disintegration of tablets.

4.1.4 Swelling: Tablets break through swelling of disintegrants [Asthana *et al.*, 2013]. Highly porous tablets show poor disintegration due to lack of adequate swelling force [Kaur *et al.*, 2011].

4.1.5 Porosity and capillary action (wicking): Penetration of water occurs when tablet comes in contact with aqueous medium, and tablet breaks (Figure 3) into fine particles by weakening of bonding force between drug particles [Panchal *et al.*, 2013].

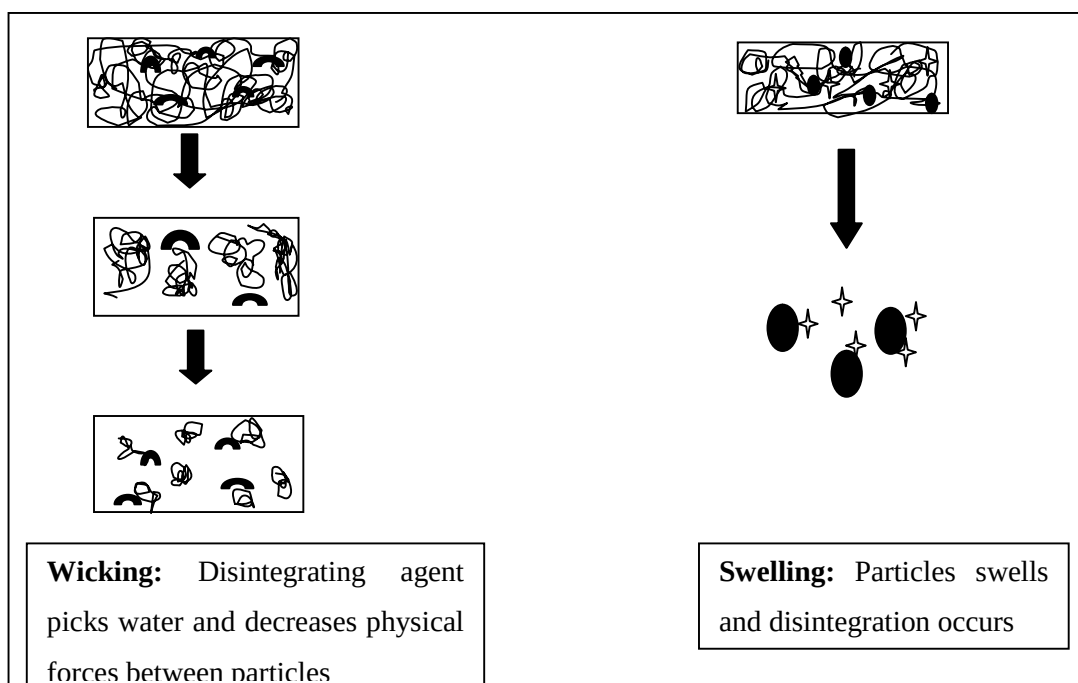
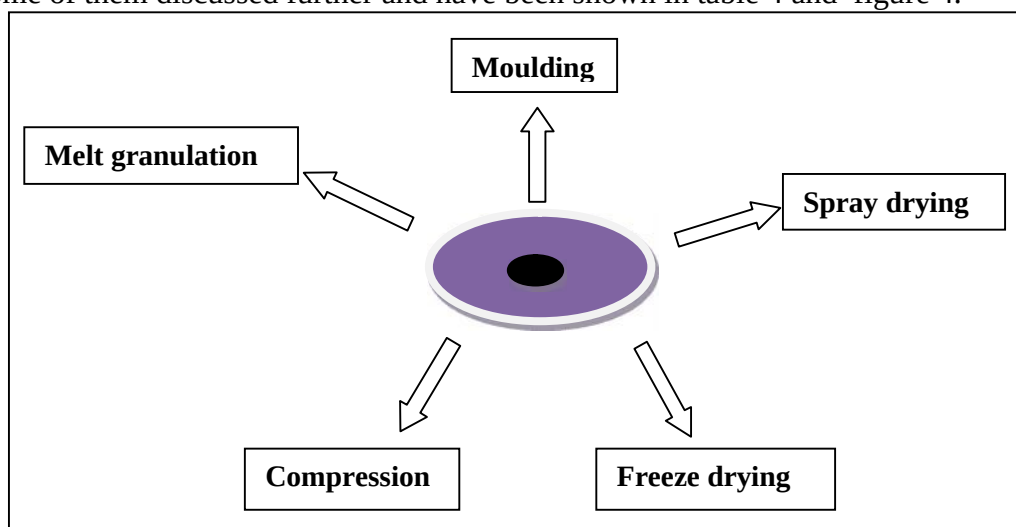


Figure 3: Disintegration phenomenon of ODT**Table 4: Formulation Techniques of Orally Disintegrating Drug Delivery System**

Conventional techniques	Patented techniques
Freeze drying	Zydis
Spray drying	Orasolv
Sublimation	Durasolv
Direct compression	Wow tab
Melt granulation	Flashtab
Molding	Flashdose
Cotton Candy Process	Ziplets

5. Conventional techniques for the preparation of ODT's : There are so many conventional technique for the preparation of ODT's which have been potentially used by the manufacturing industries. Some of them discussed further and have been shown in table 4 and figure 4.

**Figure 4: Conventional techniques of ODT formation**

5.1 Freeze drying/ Lyophilization: It involves drying at low temperature and water is removed by sublimation [Wagh *et al.*, 2010]. To dry heat sensitive drugs, this method is used [Asthana *et al.*, 2013]. Because of their high porosity and drug stability, immediate dissolution of the tablet is allowed [Sharma *et al.*, 2011]. Highly porous and light weight product is resulted by freeze-drying of drug with its additives which imparts glossy amorphous structure [Patil *et al.*, 2011]. Freeze-dried formulations provide comparatively more rapid dissolution [Nautiyal *et al.*, 2014]. This method is having the limitation that fragile tablets are produced by this method and it is difficult to handle the product as it has less mechanical strength. Under stressed conditions, they show poor stability [Patil *et al.*, 2014].

5.2 Spray drying: In this technique, highly porous and fine powder is formed by spray drying an aqueous composition consisting support matrix (gelatin) and other components (excipients) [Wagh *et al.*, 2010]. This will result in production of porous powder [Asthana *et al.*, 2013]. Then this powder is mixed with active medicament and compressed into tablets [Divate *et al.*, 2011]. Other agents like citric acid (acidic) or sodium bicarbonate (alkali) are also added to increase the disintegration and dissolution [Sreenivas *et al.*, 2005, Patil *et al.*, 2011]. Tablets which are compressed from the spray dried powder disintegrates within 20 seconds [Parashar *et al.*, 2012].

5.3 Sublimation: ODTs of very high porosity have been produced by sublimation method [Nautiyal *et al.*, 2014]. Highly water soluble ingredients usually fail to dissolve rapidly because of low porosity of the matrix [Ghosh *et al.*, 2011]. Subliming (volatile) substances such as ammonium

bicarbonate, camphor, naphthalene, urethane, urea etc. can be used to improve the porosity in tableting process [Patil *et al.*, 2011, Gupta *et al.*, 2012, Kumar *et al.*, 2012]. High porosity is achieved by forming many pores where subliming agent is present previously as subliming material is then removed by sublimation from compressed tablets [Patil *et al.*, 2014]. Solvents such as cyclohexane, benzene may be used as pore forming agents [Gupta *et al.*, 2012, Bhardwaj *et al.*, 2010, Khalid *et al.*, 2010].

5.4 Direct compression: This method is mostly used as it is cost effective and easy to implement [Wagh *et al.*, 2010, Gupta *et al.*, 2012, Shadeedi *et al.*, 2013]. Disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, effervescent agents and water soluble excipients [Patil *et al.*, 2014, Kumar *et al.*, 2012]. This method includes directly compression of tablets by mixing drug and excipients [Patil *et al.*, 2011, Patel *et al.*, 2011]. Final weight of tablet can easily be increased by adding high doses [Parashar *et al.*, 2012].

5.5 Melt granulation: In this, meltable binder is added in the pharmaceutical powders [Patil *et al.*, 2011]. PEG-6-stearate, a hydrophilic waxy binder (super polystate of melting point 33-37 °C and HLB value of 9 is added to prepare ODTs [Gupta *et al.*, 2012]. Binder usually increases the strength of tablet and helps in fast disintegration of tablet without leaving residues in oral cavity [Wagh *et al.*, 2010]. There is no drying steps as no water or other solvents are used so the process is less time consuming and uses less energy than wet granulation [Nautiyal *et al.*, 2014].

5.6 Cotton candy process: Floss-like crystalline structure is produced by spinning mechanism [Wagh *et al.*, 2010]. Polysaccharides or saccharides matrix is formed by simultaneous action of flash melting and spinning [Gupta *et al.*, 2012]. Then active ingredients and excipients are milled and blended with candy floss matrix and compressed to ODTs [Asthana *et al.*, 2013]. Larger drug doses can be accomodate and mechanical strength is improved [Nautiyal *et al.*, 2014]. As this method involves high temperature which limits its use [Patil *et al.*, 2011].

5.7 Molding: Tablets prepared by this method are solid dispersions. It is of three types: [Sharma *et al.*, 2011, Patil *et al.*, 2011]

- (a) Solvent method
- (b) Heat method
- (c) No-vacuum lyophilization

a. Solvent method: In this, the powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under low pressures (as compared to conventional tablet compression). The solvent can be removed by air drying [Patil *et al.*, 2014, Sharma *et al.*, 2011, Kalia *et al.*, 2009]. The molded tablets offer improved taste and disintegrates more rapidly [Nautiyal *et al.*, 2014]. Presence of water-soluble sugars offer improved taste [Wagh *et al.*, 2010]. Such tablets are usually less compact and possess porous structure which decreases dissolution [Patil *et al.*, 2011].

b. Heat method: It involves preparation of suspension containing agar, sugar (mannitol, lactose), drug and then pouring the suspension in blister packaging and solidifying the agar at room temperature and drying at 30 under vacuum drying [Sharma *et al.*, 2011].

c. No-vacuum lyophilisation: It involves directly preparation of molded forms from molten matrix by evaporating the solvent from the suspension at standard pressure [Patil *et al.*, 2011].

Limitation: Less mechanical strength and can undergo erosion or breakage during handling and opening of blister packs [Bangale *et al.*, 2011].

5.8 Mass extrusion: This technology involves softening of active mass by adding the solvent mixture such as water-soluble polyethylene glycol, methanol, and then the extruder or syringe is used to expel softened mass to get even cylindrical segments using heated blade [Panchal *et al.*, 2013]. Taste masking of bitter drugs can also be achieved by coating granules [Debjit *et al.*, 2009, Sharma *et al.*, 2012].

5.9 Phase transition process: In this technology, two sugar alcohols (erythritol, xylitol, trehalose, and mannitol) of high and low melting point is used to compress the tablet [Wagh *et al.*, 2010, Gupta *et al.*, 2012]. After heating process, it is seen that tablet hardness is increased due to increase in interparticle bonding and pore size of tablet, which is induced by phase transition of lower melting point sugar alcohol [Sharma *et al.*, 2012, Patil *et al.*, 2011, Gupta *et al.*, 2012].

6. Patented technologies

Various recent patents in the field of ODTs are briefly listed in Table 5 and many patented technologies are available for preparing mouth dissolving tablets. Some commercially useful technologies are discussed below:

6.1 Zydis technology: Zydis was the first marketed technique, and it is the best known of the fast dissolving tablets [Nautiyal *et al.*, 2014, Divate *et al.*, 2011]. After placing on the tongue, the tablet usually dissolves within seconds [Parashar *et al.*, 2012]. In this, the tablet is produced by lyophilizing or freeze-drying the drug in a matrix of gelatin [Ghosh *et al.*, 2011]. The freeze-dried structure disintegrates instantaneously without need of water when tablets are put into the mouth [Patil *et al.*, 2014, Gupta *et al.*, 2012]. The product should be dispensed in a special blister pack as it is very light weight and fragile [Wagh *et al.*, 2010]. However this technology has some limitations namely, it is expensive and manufacturing process is time consuming also product is less stable at higher temperatures, in humidity and stress conditions. [Wagh *et al.*, 2010]

6.2 Orasolv: Orasolv technology is patented by CIMA laboratory [Patil *et al.*, 2014]. In this taste masking of active medicament is done, and it also contains disintegrating and effervescent agent [Wagh *et al.*, 2010, Debjit *et al.*, 2009]. To minimize dissolution time, direct compression technique is used for tableting [Gupta *et al.*, 2012, Parashar *et al.*, 2012]. Wide range of active ingredients (1 mg to 500 mg) can be used [Wagh *et al.*, 2010]. Effervescent mixture is usually employed in concentration 20-25% of tablet weight [Nautiyal *et al.*, 2014, Divate *et al.*, 2011]. The widely used effervescent-disintegration pairs usually include acid sources like include adipic acid, fumaric acid, citric acid, malic acid, tartaric acid and a carbonate source include potassium bicarbonate sodium carbonate, sodium bicarbonate, and potassium carbonate [Divate *et al.*, 2011].

6.3 Durasolv: CIMA laboratory has patented this technology [Gupta *et al.*, 2012]. Tablets, in this process contain drug, lubricant and diluent [Debjit *et al.*, 2009]. This technology uses higher compaction pressures for tableting, so it has higher mechanical strength [Wagh *et al.*, 2010]. Tablets have good rigidity as conventional equipment is used [Patil *et al.*, 2014]. Durasolv can be packaged in traditional pouches, blister packaging or vials [Ghosh *et al.*, 2011].

6.4 Wow tab: The word 'wow' means without water. This technique is patented by Yamanauchi pharmaceutical company [Nautiyal *et al.*, 2014]. In this process, high saccharides (good binding property) are combined with low mouldability saccharides (rapid dissolution) and a rapidly melting strong tablet is obtained [Patil *et al.*, 2014, Debjit *et al.*, 2009]. In this, the active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and then compressed into tablet [Parashar *et al.*, 2012]. It has adequate hardness and dissolution rate [Asthana *et al.*, 2013]. Tablet usually possess sufficient hardness, and physical characteristics of formulations is maintained during production until it comes in contact with moisture such as saliva in mouth [Velmurugan *et al.*, 2009].

6.5 Flashtab: This technology is patented by Ethypharm France [Sisodiya *et al.*, 2013]. Tablets prepared by flashtab technique consists of microcrystals (carrying active ingredient) [Debjit *et al.*, 2009]. Microcrystals containing drug are prepared by using the conventional techniques like microencapsulation, coacervation, and extrusion spheronisation [Gupta *et al.*, 2012].

6.6 Flash dose: This technology was patented by Fuisz [Patil *et al.*, 2014]. In this, a sugar based matrix, called floss (combination of crystalline sugars alone or in combination with drugs) is used [Wagh *et al.*, 2010].

6.7 OraQuick

KV pharmaceutical developed a MicroMask microsphere technology based orodispersible tablet, has superior mouth feel over other taste masking options and no solvent required for taste masking process therefore production is faster and more efficient [Prabhakar *et al.*, 2012; Pandey and Dahiya 2016]. This technology also useful in the matrix system that protects the drug powder in a microencapsulated particles is more pliable, this means that the tablets can be compressed to achieve remarkable mechanical strength without disrupting taste masking [Sharma *et al.*, 2012; Fatma *et al.*, 2014].

6.8 Quick Dis technology

Lavipharm laboratories have invented an ideal oral fast-dissolving drug delivery system named as “Quick-Dis”. It is a thin, flexible mouth dissolving film that is placed on the top or the floor of the tongue and dissolve within a minute. This technology released 50% of drug within 30 second and 95% of drug within 1 min [Dobetti 2003; Pandey and Dahiya 2016]

6.9 AdvaTab technology

AdvaTab technology is developed by Eurand pharmaceuticals. This technology was patented by Kyowa Hakko Kogyo (Tokyo, Japan) and based on a proprietary tablet composition design that the lubrication is applied onto each tablet by utilizing a spray during the manufacturing process. Conventional tablets are produced using an internal lubrication system, which disperses lubricant inside and on the exterior surface of the tablets. AdvaTab is produced by using 10-30 times less hydrophobic lubricant and these tablets can be 30-40 % stronger than conventional tablets [Pandey and Dahiya 2016; Hayakawa *et al.*, 1999].

Table 5: Various recent patents in ODT field [Pandey and Dahiya 2016]

Patent Number	Title	Publication Year
EP1058538B2	Fast disintegrating tablet	2012
EP2465539A1	Disintegrating particle	2012
EP2493457A1	Fast dissolving solid	2012
US20120028949	Rapidly disintegrating tablet	2012
US20120082729	Quick dissolve compositions and tablets based thereon	2012
US20120077888	Orodispersible tablets	2012
EP2583669A1	Taste-masked orally disintegrating tablets of memantine hydrochloride	2013
EP2591774A1	Orally disintegrating tablet	2013
EP2609909A1	Mozavaptan formulations	2013
EP2595609A1	Coated effervescent tablet	2013
T0418/09	Orally disintegrating composition comprising mirtazapine	2013
WO2013072937A2	Fast release solid oral compositions of entecavir	2013

7. EVALUATIONS OF ODTs

Like any other dosage forms, oro-dispersible tablets too are evaluated for certain parameters for formulation of a stable and optimized product. These parameters (pre and postcompression parameters) are discussed below:

7.1 Precompression parameters: These include tapped density, bulk density, Carr's index, Hausner's ratio for powder blend of ODT formulations which are ready to compress into tablets.

7.1.1 Tapped density: It is denoted by the ratio of total weight of the powder to the tapped volume of the powder. Powder is tapped 750 times and if the difference between the two volumes is less than 2% then volume difference is noted. Tapping is continued for 1250 times if it is more than 2% then tapped volume is noted [Kumar *et al.*, 2013, Pandey *et al.*, 2013].

7.1.2 Bulk density: It is the ratio of total weight of powder (M) to the bulk volume (V_b) of powder. It is measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is given by

$$D_b = M / V_b$$

Where, M is the weight of powder

V_b is the bulk volume [Soni *et al.*, 2011, Pandey *et al.*, 2013].

7.1.3 Carr's index: It indicates powder flow properties. It is expressed in percentage and is given as

$$I = D_t - D_b / D_t * 100$$

Where, D_t is the tapped density of the powder, D_b is the bulk density of the powder.

7.1.4 Hausner's ratio: It denotes easiness of powder flow, it is related to inter particulate friction as such, could be used to predict powder flow properties. It is calculated by following formula [Singh *et al.*, 2012].

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

7.2. Post compression parameters:

7.2.1 Weight variation test: In this test, tablets are randomly selected and individual weight is taken. Then weight variation is checked as per specifications [Rao *et al.*, 2012, Kannuri *et al.*, 2011].

7.2.2 Thickness test: Vernier callipers is used to measure the thickness of the tablets and provides knowledge of thickness variation. The tablet thickness may also be measured by screw gauge [Rao *et al.*, 2012, Samineni *et al.*, 2013].

7.2.3 Hardness: It is an important parameter which shows resistance of the tablet to chipping, breakage and abrasion under the conditions of handling, transportation and storage [Bandari *et al.*, 2008]. Monsanto hardness tester is used for determining hardness and expressed in Kg/cm^2 [Rao *et al.*, 2012, Patel *et al.*, 2011].

7.2.4 Friability test: Mechanical strength of tablets is measured by Roche friabilator. In this test, preweighed tablets are placed in the plastic chamber of friabilator which revolves at 25rpm for 4 minutes, and then the tablets are dropped from 6 inches distance [Parashar *et al.*, 2012, Kannuri *et al.*, 2011, Kumar *et al.*, 2013, Samineni *et al.*, 2013].

7.2.5 Disintegration test: Disintegration test apparatus is used for determination of disintegration time of prepared tablets. As specified in I. P. -1996, the test is carried out on 6 tablets using the

apparatus at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$, then time is recorded for complete disintegration of tablets [Hirani *et al.*, 2009, Parashar *et al.*, 2012].

7.2.6 Dissolution test: USP paddle apparatus is used for *in vitro* dissolution studies. It is carried out at 50 rpm in 900 ml of phosphate buffer (pH 6.8), maintained at $37^{\circ}\text{C} \pm 5^{\circ}\text{C}$. At regular intervals, 5 ml of sample is withdrawn and assayed spectrophotometrically [Farshid *et al.*, 2014].

7.2.7 Wetting time: It represents the time taken for the tablet to disintegrate when kept motionless on the tongue. In this test, the tablet is placed on a piece of tissue paper folded double in a petri plate (internal diameter is 6.5 cm) containing 6 ml of water. Then the tablet's complete wetting time is noted. The test is carried out at 37°C [Kela *et al.*, 2013, Bhowmik *et al.*, 2009 Kumar *et al.*, 2013].

7.2.8 Stability study: It may be defined as the capacity of a drug substance or product to remain within the specifications provided to maintain its identity, strength, quality and purity throughout the expiration dating period [Sisodiya *et al.*, 2013, Patel *et al.*, 2011].

Conditions for accelerated studies as prescribed by ICH guidelines are:

- (i) $40 \pm 1^{\circ}\text{C}$
- (ii) $50 \pm 1^{\circ}\text{C}$
- (iii) $37 \pm 1^{\circ}\text{C}$ and RH $75\% \pm 5\%$

After a period of 15 days, the tablets are withdrawn and analyzed for physical characterization [Sharma *et al.*, 2012, Parashar *et al.*, 2012, Ponugoti *et al.*, 2014, Chaturvedi *et al.*, 2011, Gandhi *et al.*, 2012].

8. Limitation of ODTs

Most of times the tablets have insufficient mechanical strength hence, careful handling is necessary. Specialized packing might be required for hygroscopic and light sensitive drugs because when soluble diluents were used for formulating ODTs might render hygroscopic dosage which may lead to stability issues. The tablets may leave an unpalatable taste and grittiness in the oral cavity if not formulated properly is the main drawback of ODTs [Pandey and Dahiya, 2016; Rewar *et al.*, 2014].

9. FUTURE PROSPECTS OF ODTs

ODTs provide advantageous dosage forms for the oral drug delivery of certain drugs which have limited bioavailability such as protein and peptide-based therapeutics. ODTs usually offers many biopharmaceutical advantages such as faster onset of action, improved efficiency over conventional dosage forms, less side effects etc. Low drug dose is required and is found to be more effective than conventional dosage forms like tablets and capsules, and it is observed that this small dose shows better bioavailability and improved dissolution profiles.

10. CONCLUSIONS

ODTs is a developing technology and it offers many advantages for lifecycle management, patient convenience, market shares and development timelines. Close attention must be paid to develop advancement in technologies to formulate ODTs, so that pharmaceutical companies may take advantage of developed techniques for extending market values of ODTs. Patient compliance, rapid onset of action, low dosing, fast disintegration, better stability, less side effects and ultimately popularity in near future will surely be enhanced by the availability of many technologies and the desired advantages of ODTs. Today, ODTs are widely available for the treatment of motion sickness, traveller's diarrhoea, common cold, allergies and flu symptoms.

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