REVIEW ARTICLE

Orodispersible tablets: An overview

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Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop orally disintegrating tablets (ODTs) with improved patient compliance and convenience. ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This review describes the various formulation aspects, disintegrants employed and technologies developed for ODTs, along with various excipients, evaluation tests, marketed formulations, and drugs explored in this field.

Key words: *Disintegration, lyophilization, orodispersible tablets, superdisintegrants*

INTRODUCTION

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia[1] (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications.[2] ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.[3]

United States Food and Drug Administration (FDA) 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 for ODTs generally ranges from several seconds to about a minute.

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SIGNIFICANCE

Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include:

i. As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.[4-7]
ii. No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water.
iii. Easy to administer for pediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients)
iv. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.[8]
v. Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.
vi. Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased.[9-11]
vii. Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.[12]

CHALLENGES TO DEVELOP ODT

i. Rapid disintegration of tablet
ii. Avoid increase in tablet size
iii. Have sufficient mechanical strength

iv. Minimum or no residue in mouth
v. Protection from moisture
vi. Good package design
vii. Compatible with taste masking technology
viii. Not affected by drug properties

FORMULATION ASPECTS IN DEVELOPING ODT

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as,

i. Mechanical strength of tablets
ii. Taste and mouth feel
iii. Swallowability
iv. Drug dissolution in saliva
v. Bioavailability
vi. Stability

Various processes employed in formulating ODTs include freeze-drying, cotton candy process, molding, spray drying, mass extrusion, and compaction. Table 1 enlists various drugs explored for developing ODTs.

LYOPHILIZATION OR FREEZE-DRYING

Formation of porous product in freeze-drying process is exploited in formulating ODT. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug.

Several technologies are patented involving lyophilization process, which are discussed in this article. However, the ODTs formed by lyophilization has low mechanical strength, poor stability at higher temperature, and humidity.[5] Along with above complications and its expensive equipment freeze-drying use is observed to be limited.

MOLDING

Molding process includes moistening, dissolving, or dispersing the drug with a solvent then molding the moist mixture into tablets (compression molding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution, or suspension at ambient pressure (no vacuum lyophilization), respectively.[13]

The molded tablets formed by compression molding are air-dried. As the compression force employed is lower than conventional tablets, the molded tablet results in highly porous structure, which increases the disintegration and dissolution rate of the product. However, to further improve dissolution rate of the product powder mixture should be sieved through very fine screen. As molding process is employed usually with soluble ingredients (saccharides) which offers improved mouth feel and disintegration of tablets. However, molded tablets have low mechanical strength, which results in erosion and breakage during handling.[58]

COTTON CANDY PROCESS

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process[14] involves formation of matrix of polysaccharides or saccharides by

Table 1: Drugs explored for orally disintegrating tablet[3,8,10,11,12,46,48,59,60-66]

Category	Drug	Category	Drug
NSAIDS	Ketoprofen	Anti depressants	Mitraxepine
	Piroxicam		Fluoxetine
	Paracetomol		
	Rofecoxib	Antiparkinsonism	Selegiline
	Nimesulide		
	Ibuprofen	Antimigrane	Sumatriptan
	Tepoxaline (Canine NSAID)		Rizatriptan benzoate
Anti ulcer	Famotidine		Zolmitriptan
	Lansoprazole		
Anti histaminics	Loratadine	Antiemetics	Ramosetoron Hcl
	Diphenhydramine		Ondansetron
	Meclizine	Miscellaneous	Baclofen
Hypnotics and sedatives	Zolpidem		Hydrochlorthiazide
	Clonazepam		Ethenzamide
	Atenolol		Tramodol Hcl
Antpsychotics	Olanzepine		Propyphenazone
	Risperidone		Spiranolactone
	Pirenzepine		Phloroglucinol
			Sildenafil

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.

SPRAY DRYING

Highly porous, fine powders are obtained by this method. Allen *et al.*[15] utilized this process for preparing ODT. The ODT formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid (an acid) and sodium bicarbonate (an alkali). The formulation was spray dried to yield a porous powder. The ODT made from this method disintegrated in <20 s.[16,17]

MASS EXTRUSION

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets.[18]

COMPACTION

Melt granulation

Abdelbary *et al.*[19] prepared ODT by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Superpolystate is a waxy material with an m.p. of 33-37°C and an hydrophilic lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue.

Super polystate was incorporated in the formulation of ODT by melt granulation method where granules are formed by the molten form of this material. Crystallized paracetamol was used as model drug and in addition the formulation included mannitol as a water-soluble excipient and crosscarmellose sodium as disintegrating agent.

Phase transition process

Kuno *et al.*[20] investigated the disintegration of ODT by phase transition of sugar alcohols using erythritol (m.p. 122°C), xylitol (m.p. 93-95°C), trehalose (97°C), and mannitol (166°C).

Tablets were produced by compressing a powder containing two sugar alcohols with high- and low-melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

Sublimation

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODT. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet.

Koizumi *et al.*[21] developed ODT utilizing camphor, a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.

Conventional methods

Conventional methods in formulating tablets such as dry granulation,[22] wet granulation,[23] and direct compression methods were adapted to produce ODTs. In formulating ODTs, one of the important components is the super disintegrants. Several excipients are investigated for rapid disintegration of ODTs, some of the super disintegrants employed are discussed in Table 2.

PATENTED TECHNOLOGIES

Zydis technology[4]

Zydis is patented by R.P. Scherer. This technology includes physical trapping of the drug in a matrix composed of a saccharide and a polymer.[24,25] Polymers generally employed are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, polyvinyl alcohol, polyvinyl pyrrolidine, acacia, and these mixtures. The methodology involves solution or dispersion of components is prepared and filled in to blister cavities, which are frozen in a liquid nitrogen environment. The frozen solvent is removed or sublimed to produce porous wafers. Peelable backing foil is used to pack Zydis units. Zydis formulation is sensitive to moisture and may degrade at humidity greater than 65%.

Desired characteristics of Zydis technology

i. Drug should be chemically stable
ii. Water insoluble
iii. Particle size should be smaller than 50 μm.
iv. Dose for water-soluble drugs is limited (60 mg)

Lyoc[26]

Lyoc technology is patented by PHARMALYOC. Oil in water emulsion is prepared and placed directly into blister cavities

Table 2: Super disintegrants employed in orally disintegrating tablet[55,57]

Super disintegrant	Nature	Properties	Mechanism
Crosspovidone	Crosslinked homo polymer of *N*-vinyl-2-pyrrolidone	Particle size - 100 µm Insoluble in water Gives smoother mouth feel	Both swelling and wicking
Cross carmellose sodium	Cross-linked form of sodium CMC	Particle size 200 mesh Insoluble in water	Swelling
Sodium starch glycolate	Crosslinked low substituted carboxymethyl ether of poly-glucopyranose	Particle size 140 mesh Insoluble in organic solvents, disperses in cold water and settles in the form of a highly saturated layer	Water uptake followed by rapid and enormous swelling
Acrylic acid derivatives[55] (Yang *et al*. 2004)	Poly(acrylic acid) super porous hydrogel	Particle size 106 µm DT - 15 + 2 S	Wicking action
Effervescent mixture	Citric acid, tartaric acid, sodium bicarbonate	Crystalline nature	Effervescence
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water, hygroscopic in nature	Swelling
NS-300[57] (Ozeki *et al.* 2003)	Carboxy methyl cellulose	Particle size 106 µm DT - 20 S	Wicking type
ECG-505[57] (Ozeki *et al.* 2003)	Calcium salt of CMC	Particle size 106 µm DT - 80 S	Swelling type
L-HPC[57] (Ozeki *et al.* 2003)	Low hydroxy propyl cellulose	Particle size 106 µm DT - 90 S	Both swelling and wicking

followed by freeze-drying. Nonhomogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

Quick solv[27]

This technology is patented by Janssen Pharmaceuticals. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

Nanocrystal technology[28]

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. As manufacturing losses are negligible, this process is useful for small quantities of drug.

Flashtab technology[29]

This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types.

Disintegrating agents include reticulated polyvinylpyrrolidine or carboxy methylcellulose. Swelling agents include carboxymethylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min.

Orasolv technology[30,31]

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the ODT. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight.

As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv,[32] a special packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet with in the depression. Paksolv offers moisture, light, and child resistance packing.

Durasolv technology[33]

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants.

Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in bottles and blisters. Nondirect compressible fillers generally used in the range of 60-95%, lubricant in 1-2.5%.

WOW tab technology[34,35]

Yamanouchi patented this technology. WOW means with out water. This technology utilizes conventional granulation and tableting methods to produce ODT employing low- and high-moldability saccharides.

Low moldability saccharides are lactose mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration.

Dispersible tablet technology[36]

Lek, Yugoslavia patents this technology. It offers development of ODT with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration.

Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrants improved disintegration of tablets usually less than 1 min.

Pharmaburst technology[3]

SPI Pharma, New Castle, patents this technology. It utilizes the coprocessed excipients to develop ODT, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

Frosta technology[3]

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of:

i. Porous and plastic material,
ii. Water penetration enhancer, and
iii. Binder.

The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 s depending on size of tablet.

Oraquick

This technology is patented by K.V Pharmaceuticals.[37] It utilizes taste masking microsphere technology called as micromask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This process involves preparation of microparticles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat-sensitive drugs. Oraquick product dissolves within few seconds.

Ziplets/advatab[38]

This technology is patented by Pessano con Bornago, 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.

Flashdose[39,40]

Fuisz has patented Flashdose technology. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flashdose technology is the first commercial product launched by Bioavail Corporation. Flashdose tablets consist of self-binding shearform matrix termed as "floss." Shearform matrices are prepared by flash heat processing.

There are several commercial products available in national and international market for orally disintegrating tablets that are given in Tables 3 and 4.

Approaches for masking taste

Orally disintegrating tablet, which disintegrate or dissolve in the saliva and produce a positive or negative taste sensation. Most of the drugs have unpalatable taste in which taste masking plays critical role in formulating ODT.

The negative taste sensation of drugs can be reduced or eliminated by various approaches studied, which include addition of sweeteners and flavors, encapsulating the unpleasant drug in to microparticles and adjustment of pH.

Table 3: Orally disintegrating tablet products available in Indian market

Brand name	Active ingredient	Company
Domray MD	Domperidone	Ray Remedies
Velrid MD	Domperidone	Shreyam Health Care
Vomidon MD	Domperidone	Olcare Lab
Zotacet MD	Cetirizine Hcl	Zota Pharma
Olanex Instab	Olanzepine	Ranbaxy
Manza RDT	Olanzepine	Mano Pharma (Orchid)
Romilast	Montelukast	Ranbaxy
Torrox MT	Rofecoxib	Torrent
Ziflam	Rofecoxib	Kopran
Doloroff	Rofecoxib	Indoco
Rofaday MT	Rofecoxib	Lupin
Dolib MD	Rofecoxib	Panacea
Orthoref MD	Rofecoxib	Biochem
Rbcox-25 MD	Rofecoxib	Shalman Pharma
Roffec MD	Rofecoxib	Excare Lab
Roftab MD	Rofecoxib	Olcare Lab
Zofex-25 MD	Rofecoxib	Zota Pharma
Valus	Valdecoxib	Glenmark
Nency MD	Nimesulide	Zenon Health Care
Nexus MD	Nimesulide	Lexus
Nimex MD	Nimesulide	Mexon Health Care
Nimez-MD	Nimesulide	Zota Pharma
Nisure-MD	Nimesulide	Suzen Pharma
Nimulid-MD	Nimesulide	Panacea
Olnim-MD	Nimesulide	Olcare Lab
Sulbid-Md	Nimesulide	Alpic remedies
Topmide	Nimesulide	Antigen Health Care
Nimpain MD	Nimesulide	Prompt Cure Pharma
Mosid MT	Mosapride	Torrent

Incorporation of sweeteners and flavors

Maximum patient acceptability with ODT is seen if they provide pleasant taste and mouth feel. To provide this property in tablets various sweeteners and flavors are employed. Usually sugar-based excipients are used as they are highly water soluble and dissolve quickly in saliva and provide pleasant taste and mouth feel to the final product.[41]

Mannitol is most widely used excipient in formulating ODT. Aspartame and citric acid are most commonly used along with various flavorants such as mint flavor orange flavor, strawberry flavor, peppermint flavor to produce pleasant taste, and mouth feel.

Encapsulation or coating of drugs

Some of the unpleasant drugs cannot be masked by incorporation of sweeteners and flavors, in such cases alternative method of masking the taste is by encapsulating or coating the drug. In fact this process retards or inhibits dissolution and solubilization of drug, which allows time for particles to pass form mouth before taste is perceived in mouth.[42]

Various techniques utilized include

i. CIMA'S taste masking technique uses coating of drug with dissolution retarding material.[43]
ii. Phase separation approach for taste-masked microcapsules.[44]
iii. Microcaps process used microencapsulation technology.[45]
iv. Extrusion method.
v. Micromask technology used casting or spin congealing melt dispersions or solution of drug in molten blend of materials.[3]
vi. Flashtab technology.[29]
vii. Solutab technology involves coating drug with sustained release agents, which are finally coated with enteric polymers and further with mannitol.[46]
viii. Blending with cyclodextrins.[47]
ix. Coating crystals, granules, and pellets with aqueous dispersions of methacrylic acid polymers.

Evaluation of ODTs

Evaluation parameters of tablets mentioned in the pharmacopoeias need to be assessed, along with some special tests are discussed here.

Hardness/crushing strength

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for an ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The crushing strength of the tablet may be measured using conventional hardness testers.

Friability

To achieve % friability within limits for an ODT is a challenge to the formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

Wetting time and water absorption ratio

Wetting time of dosage form is related with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet.

The wetting time of the tablets can be measured using a simple procedure.[48] Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10-cm diameter. Ten milliliters of water-soluble dye (eosin) solution is added to 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 (W_b). The wetted tablet from the petridish is taken and reweighed (W_a). The water absorption ratio, *R* can be then determined according

Table 4: Orally disintegrating tablet products available in international market

Brand name	Active ingredient	Company
Zomig ZMT and Rpimelt	Zolmitriptan	Astra Zeneca
Alavert	Loratadine	Wyeth Consumer Healthcare
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	ETHEX Corporation
NuLev	Hyoscyamine sulfate	Schwarz Pharma
Nurofen FlashTab	Ibuprofen	Boots Healthcare
Kemstro	Baclofen	Schwarz Pharma
Fluoxetine ODT	Fluoxetine	Bioavail
Benadryl Fastmelt	Diphenhydramine	Pfizer
Zolpidem ODT	Zolpidem tartrate	Bioavail
Nasea OD	Ramosetoron	Yamanouchi
Ralivia FlashDose	Tramadol HCL	Bioavail
Gaster D	Famotidine	Yamanouchi
Excedrin Quick Tabs	Acetaminophen	Bristol-Myers Squibb
Claritin RediTabs	Loratadine	Sching Corporation
Remeron SolTab	Mirtazepine	Organon Inc.
Feldene Melt	Piroxicam	Pfizer
Tempra Quicklet-Tempra Firs Tabs	Acetaminophen	Bristol-Myers Squibb
Maxalt-MLT	Rizatriptan benzoate	Merck
Propulsid Quicksolv	Cisapride monohydrate	Janssen
Pepcid ODT	Famotidine	Merck
Imodium Instant melts	Loperamide HCL	Janssen
Zyprexa	Olanzapine	Eli Lilly
Childrens Dimetapp ND	Loratadine	Wyeth Consumer Healthcare
Zofran ODT	Ondansetron	Glaxo Smith Kline
Klonopin Wafers	Clonaxepam	Roche
Risperidal M-Tab	Ripseridone	Janssen
Zelapar	Selegiline	Élan/Amarin Corporation
Zubrin (pet drug)	Tepoxaline	Schering Corporation
Aricept ODT	Donepzil HCL	Eisai and Pfizer
Fazalco	Clonzapine	Alamo Pharmaceuticals
Permax	Pergolide	Amarin Corporation
Febrectol	Paracetamol	Prographarm
Benadryl Fast melt	Diphenhydramine and psuedoephedrine	Warner Lambert

to the following equation:

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

Moisture uptake studies

Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37°C for 24 h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrant) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Disintegration test

The time for disintegration of ODTs is generally <1 min and actual disintegration time that patient can experience ranges from 5 to 30 s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents. Various disintegration methods developed are discussed in Table 5.

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 1 and 2 can be used. USP 1 Basket apparatus may have certain applications, but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the

Table 5: *In vitro* disintegration methods for orally disintegrating tablet

In vitro disintegration method	Characteristic features	Critical parameters	Referenes
Modified USP Apparatus II	One liter cylindrical vessel, Paddle as stirring element, basket sinker with ODT was placed in middle of vessel and hang by a hook to the lid of vessel with distance of 6-8.5 cm	Medium 900 ml, Temp 37°C, Paddle, 100 rpm	Sunada and Bi Y. 2002; Bi *et al.* 1996[50, 56]
Rotary shaft method	Stainless steel wire gauze on which ODT is placed and slightly immersed in medium. Rotary shaft is employed to provide mechanical stress and rotation	Rotational speed, Mechanical stress	Narazaki *et al.* 2004[54]
Sieve method	Glass cylinder with 10-mesh sieve. Device is placed in shaking water bath operated at 150 rpm	Medium 1 ml, Temp. 37°C, Shaking speed of water bath	Fu *et al.* 2003[52]
Texture analyzer	Cylindrical flat probe, the bottom of which is adhered by ODT, which was attached to load cell with very thin layer of glue. ODT submerged in medium present in beaker or petridish and compressed. Distance traveled by probe into tablet is measure of disintegration time	Force of compression, medium 0.4 ml water. Room temperature, measures beginning and ending of disintegration time	Dor and Fix. 2002[51]
Charge coupled device method	Disintegration component and measurement device, which involve continuous acquisition of picture by CCD camera to record disintegration. Plastic cell divided in two parts one component inner tank containing stirring bar, second component is outer tank of thermo stated water	Medium 200 ml, Temp. 37 ± 2°C	Mortia *et al.* 2002[53]

spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. Kancke[49] proposed USP 2 Paddle apparatus, which is the most suitable and common choice for ODTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of ODT is very fast when using USP monograph conditions; hence, slower paddle speeds may be utilized to obtain a profile.

The USP 2 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 analyze dissolution aliquots due to presence of UV absorbing components, specifically flavors and sweetener. Excipient to drug ratio may be higher since the formulation is designed to have good taste and mouth feel, decreasing the detection of the drug to background (excipient) in the UV spectrophotometer.

Packaging of ODT

Packing is one of the important aspects in manufacturing ODT. The products obtained by various technologies vary in some of the parameters especially in mechanical strength to a good extent. The products obtained by lyophilization process including various technologies such has Zydis, Lyoc, Quicksolv, and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture, and may degrade at higher humidity conditions. For the above reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Paksolv is a special packaging unit, which has a dome-

shaped blister, which prevents vertical movement of tablet with in the depression and protect tablets from breaking during storage and transport, which is used for Orasolv tablet. Some of the products obtained from Durasolv. WOW Tab, Pharmaburst oraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles.

Patient counseling in effective use of ODT

ODT developed offers significant advantages for various group of patients, but the majority of patients receiving ODT have little understanding of this novel dosage form. Patients receiving ODT may be surprised when tablets begin to disintegrate/dissolve in mouth. As pharmacists are ideal persons to know about the recent technologies, thus have opportunity to educate the patients for effective treatment.

Counseling of patients about this dosage form can avoid any confusion and misunderstanding in taking ODT. Patient information that need to be provided include:

- Storage of this dosage form as some of ODT developed may not have sufficient mechanical strength, which needs to be handled carefully.
- Patients with Siogren's syndrome or dryness of mouth or who take anticholinergic drugs may not be suitable candidates for administering ODT. Although no water is required to allow drug to disperse quickly and efficiently but decreased volume of saliva may slow the rate of disintegration/dissolution and may reduce the bioavailability of the product.
- Patients need to be clearly told about the difference between effervescent and ODT. Some of technologies use effervescence, which experience a pleasing tingling effect on the tongue.
- Although chewable tablets are available in market and patient need to be counseled about differences between chewable and ODT tablets. This ODT can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently.

With the pharmacists counseling, intervention and assistance about ODT, all patients receiving this novel dosage form could be more properly and effectively treated with greater convenience.

CONCLUSIONS

The ODTs have potential advantages over conventional dosage forms, with their improved patient compliance; convenience, bioavailability and rapid onset of action had drawn the attention of many manufactures over a decade. ODT formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. This ODT can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently which made them popular. As they have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. Thus ODT may be developed for most of the available drugs in near future.

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