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Review Article

Recent advances in orodispersible tablets: A Review

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Abstract

During the last decade, several new advanced technologies have been introduced for the formulation of ODTs (Orodispersible Tablets) with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients. Recent advances means that how much new technique has been developed in the filed of pharmacy for the orally dispersible tablet. From the pharmaceutical industry's point of view, ODTs can provide new dosage forms as a life cycle management tool for drugs near the end of their patent life. Orodispersible are known by various names such as mouth dissolving, fast dissolving, fast melting, and rapidly disintegrating, orally disintegrating tablets.

Keywords: Orodispersible, Disintegration time, diabetic.

Introduction

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). The reason for this paradigm shift may be due to relatively low development cost and time required for introducing a NDDS ($ 20-50 million and 3-4 years respectively) as compared to a new chemical entity (approximately $ 500 million and 10-12 years, respectively). In the form of NDDS, an existing drug molecule can get a 'new life', thereby increasing its market value, competitiveness, and patent life. Among the various NDDS available in market, orodispersible tablets hold the major share because of their obvious advantages of ease of administration and better patient compliance. Difficulty in swallowing a tablet or capsule is a common problem of all age groups, especially of elderly and paediatrics, because of physiological changes associated with these groups of patients. These problems led to the development of novel type of solid oral dosage form called "orodispersible tablet". ODTs are known by various names such as mouth dissolving, fast dissolving, fast melting, and rapidly disintegrating, orally disintegrating tablets. The European pharmacopoeia defines the term "orodisperse" as a tablet that can be placed in the mouth where it disperses rapidly before swallowing [1]. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction [2]. Such a tablet disintegrates instantaneously when placed on tongue, releases the drug that dissolves or disperses in the saliva. As the oral mucosa is highly vuscularised [3], drugs that are absorbed through the oral mucosa can directly enter into the systemic circulation, bypassing the gastrointestinal tract (GIT) and therefore first-pass metabolism in the liver. This result to a rapid onset of action [4], and greater bioavailability of the drug than those observed from conventional tablet dosage form [5].

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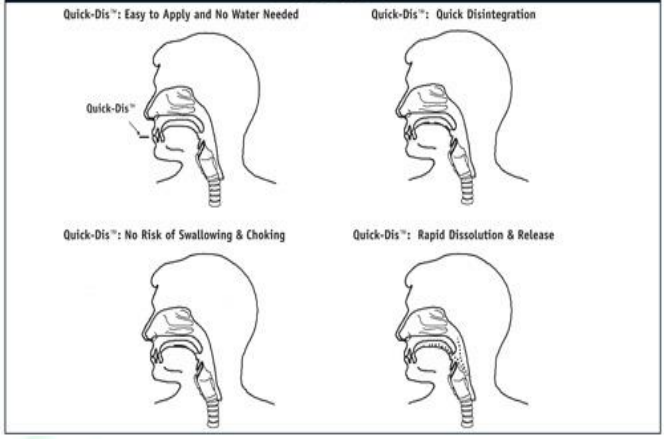
Various technologies utilized for fabrication of ODTs and these techniques are based on the principles of increasing porosity by addition of superdisintegrants and/or water soluble excipients in the tablets.

Advantages Of ODTs

ODTs have the advantages of ease of administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure and who refuse to swallow such as paediatric, geriatric and psychiatric patients. No need of water to swallow the dosage form, which is highly convenient for patients who are travelling and do not have immediate access of water.. Because, the tablets disintegrate inside the mouth, drugs may be absorbed from the pregastric area i.e., mouth, pharynx and oesophagus which may produce rapid onset of action [6,7] prevent loss of drug due to first-pass effect. Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects[8].

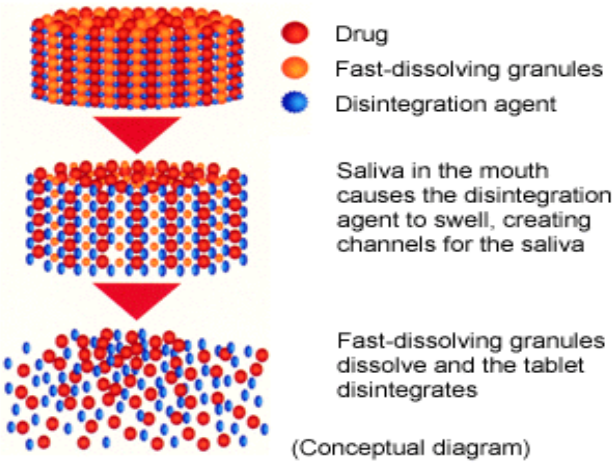
FIGURE 1



Characteristics And Formulation Challenges Of ODTs

The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows water absorption faster with maintenance of higher mechanical strength. ODTs should have low sensitivity to moisture for greater stability. A good package design or other strategy should be created to prevent ODTs from various environmental conditions [2]. For the ideal ODTs technology, the drug properties should not significantly affect the tablet property for example; the solubility, crystal

morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final characteristics of tablets, such as porosity, tablet strength, disintegration and dissolution As the ODTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. Thus, the taste inside the mouth becomes critical for patient acceptance. When the drug is tasteless or does not have an undesirable taste, taste masking techniques does not become so important. The taste masking technology should not affect the ODT formulation.



COMMERCIALLY AVAILABLE ODT PRODUCTS

Trade name	Active ingredient	Manufacturer
Rofaday MT	Rofecoxib	Lupin
Torrox Mt	Rofecoxib	Torrent
Mosid MT	Mosapride	Torrent
Values	Valdecoxib	Glenmark
Olanex Instab	Olanzepine	Ranbaxy
Zyprexa	Olanzapine	Eli lilly
Cibalginadue FAST	Ibuprofen	Novartisconsumer health
Benadryl Fastmelt	Diphenhydramine	Pfizer
Feldene melt	Piroxicam	Pfizer

Techniques For Preparing ODTs

The various techniques are being utilized or adopted to prepare ODTs

a) Direct Compression
b) Sublimation
c) Humidity treatment
d) Sintering
e) Wet Granulation
f) Dry Granulation
g) Melt Granulation
h) Spray Drying
i) Moulding
j) Freeze Drying

A) Direct Compression

This technique can now be applied for preparation of ODT, because of the availability of improved excipients especially superdisintegrants and sugar based excipients. The introduction of superdisintegrants has increased the popularity of this technology.[9] However, above the critical concentration level of disintegrant, disintegration time remains approximately constant or the decrease is insignificant[10]. Bi et al.[11] and Watnabe[12] used microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) to manufacture ODTs wherein the ratio of MCC to HPC varied from 8:2 to 9:1. Another approach to manufacture ODTs by direct compression is the use of sugar-based excipients (dextrose, fructose, isomalt, maltose, mannitol, sorbitol, xylitol) which display high aqueous solubility and sweetness and hence, imparts taste masking and a pleasing mouth feel.

B) Sublimation

When volatile materials are compressed into tablets using the conventional method, they can be removed via sublimation, resulting in highly porous structures. The volatile materials include urea, ammonium carbonate, ammonium bicarbonate, hexa methylene tetramine, and camphor. Heinemann[13] disclosed a process to prepare porous tablets by sublimation. The mixtures of volatile adjuvents were made into tablets and subsequently heated. The volatile ingredient while leaving the core of tablet makes pores into it.

c) HUMIDITY TREATMENT

The mechanical strength of some tablets increased substantially after moisture treatment, compared with the tablets before the treatment. The increase is known to be due to the formation of liquid bridges in the presence of moisture and then formation of solid bridges after drying. When an amorphous sugar is treated to go through the humidification and drying process, it changes to a crystalline state. This change increases the tablet strength substantially.[14, 15]

In a patent by Mizumoto et al [15] a drug, a sugar, and an amorphous sugar capable of transforming from amorphous to crystalline state were mixed and compressed into tablets. The "amorphous sugar" is those that can form an amorphous state by spray drying, freeze drying, or other granulation methods. These amorphous sugars include glucose, lactose, maltose, sorbitol, trehalose, lactilol, and fructose. The relative humidity is determined by the apparent critical relative humidity of the mixture of a drug and an amorphous sugar. A relative humidity greater than or equal to the critical relative humidity of this mixture is chosen for the humidity condition. The advantage of using amorphous sugar is that they have low critical relative humidity, so that they can absorb water even at low moisture levels. If a high humidity condition is used, tablets may adhere together, causing manufacturing problems.

D) Sintering

When thermal energy is applied to a powder compact, the compact is densified and the average grain size increases. The basic phenomena occurring during this process, called sintering, are densification and grain growth. Lagoviyer et al[16] disclosed a process that tablet strength can be increased by sintering the tablet components at high temperatures and then resolidifying them at lower temperatures. A bulk agent in this formulation is used to provide bulk volume to the overall tablet, and suitable agents include carbohydrates, calcium carbonate, and magnesium carbonate. Solvents can be chosen from water, ethyl alcohol, isopropyl alcohol, or a mixture thereof. Binders are

water soluble polymers such as polyethylene glycol (PEG), with a molecular weight of approximately 1000 to 1,000,000 Dalton. The granules are then lightly compressed to form tablets. These tablets are heated for a sufficient time and temperature to allow the binding agent to melt. The heating step is intended to melt the binding agent to create intra tablet bonds and help weld the product shape together. Typically, a laboratory oven is set at around 50-100ºC. The heating time ranges from 3 to 45 minutes. The binding agents are resolidified as the temperature is reduced to ambient temperature. The disintegration time is generally within 3-60 seconds.

E) Wet Granulation

Bonadeo et al[17] described a process of producing ODTs by wet granulation in a fluidized bed. The formulation includes polyalcohols (e.g., mannitol, xylitol, sorbitol, maltilol, erythritol, and lactilol), 1-30% of an edible acid, and an active ingredient as the dry mixture. This mixture was wet granulated with an aqueous solution of a water-soluble or water-dispersible polymer (e.g., polyethylene glycols, carrageenan, and ethyl cellulose), which consisted of 1-10% of the final weight of the granule in a fluid bed. Granules with high porosity and low apparent density were obtained, and the tablets made by such granules had rapid disintegration times ranging from 3 to 30 seconds in the saliva.

F) Dry Granulation

Eoga and Valia[18] disclosed a method of preparation of ODTs by dry granulation. Low density alkali earth metal salts or water soluble carbohydrates were precompacted, and the resulting granules were compressed into tablets that could dissolve fast. In this process, a powdered material with a density of 0.2 to 0.55 gm/ml was precompacted to increase the density to 0.4 to 0.75 g/ml by applying pressure ranging from 1 to 9 kN/cm. The resulting granules were compressed into tablets.

G) Melt Granulation

Abdelbery et al[19] described a new approach of preparing ODTs with sufficient mechanical strength, involving the use of a hydrophilic waxy binder (SuperpolystateR, PEG-6-stearate) by melt granulation or wet granulation. In case of melt granulation granules were prepared in a high speed blade mixer at 40-44ºC, according to the conventional hot melt procedure. For wet granulation, an oil in water emulsion of SuperpolystateR was used as the granulating agent. Then, granules were blended with croscarmellose, aspartame, and magnesium stearate and compressed into tablets. The melt granulation ODTs had better hardness results than the wet granulation ODTs. The disintegration times of melt granulation tablets, however, was more than one minutes.

H) Spray Drying

Spray drying technique produces highly porous and fine powders as the processing solvent is evaporated during this process. Allen et al[20] have used spray-drying for the production of ODTs.The formulations contained hydrolyzed and nonhydrolyzed gelatin (same net charge) as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscarmellose as a disintegrant. To maintain the net charges of the gelatin, an acidifying or alkalinizing agent was included. The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in less than 20 seconds in aqueous medium.

I) Moulding

Moulded tablets contain water soluble ingredients due to which the tablets dissolve completely and rapidly. Moulding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressure in moulded plates to form a wetted mass. The solvent is then removed by air drying. The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 300˚C under vacuum. Pebley et al[21] evaporated the frozen mixture containing a gum(e.g. acacia, carageenan, guar, tragacanth or xanthan), a carbohydrate (e.g. dextrose, lactose, maltose, mannitol or maltodextrin) and solvent in a tablet-shaped mould to design a ODT with a disintegration time of about 20-60 seconds.

J) Freeze Drying

In freeze drying process, the water is sublimed from the product after it is frozen. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. After freeze drying the aluminium foil backing is applied on a blister sealing machine. Jaccend and Leyder[8] used freeze drying to develop an oral formulation of several drugs such as spiranolactone and trolendomycin. Corveleyn and Remon[5, 21] studied various formulations and process parameters by using hydrochlorothiazide as a model drug.

Patented Technologies For ODTs

a) Zydis technology

Zydis is a unique freeze dried oral solid dosage form that can be administered without water and it dissolves instantly on the tongue in less than 3 seconds. The drug is physically trapped in a water soluble matrix, and then freeze dried to produce a product that rapidly dissolves. The matrix usually contain excipients like polymers (e.g., gelatin, alginates, and dextrin) to provide strength and rigidity to tablets; polysaccharides(e.g., mannitol and sorbitol) to impart crystallinity and hardness to the matrix and to improve palatability; collapse protectants(e.g., glycine) to prevent the product from shrinking in its packaging during manufacturing or storage; flocculating agents(e.g. xanthan gum and acacia) to provide uniform dispersion of drug particles; preservatives(e.g., parabens) to prevent microbial growth; permeation enhancers(e.g., sodium lauryl sulphate) to improve transmucosal permeability; pH adjusters(e.g., citric acid) to optimize chemical stability; flavours and sweetners to improve patient compliance and water to ensure formation of porous units. Thirteen products are currently available based on zydis technology.[23] In US, the zydis products available are Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT, and Zyprexa Zydis. In the worldwide market, zydis formulations are also available for oxazepam, lorazepam, loperamide, and enalapril [24].

CIMA (certified investment management analyst) labs have developed orasolv technology [25]. It uses an effervescent agent that releases gas upon contact with water. Effervescent agent usually includes an acid source and a carbonate source. The acid sources include citric acid, tartaric acid, maleic acid, fumaric acid, adipic acid, and succinic acids. The carbonate sources include sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate. Tablets are prepared by direct compression at low compression force in order to

minimize oral disintegration time. The active medicaments are taste masked and dispersed in saliva due to the action of effervescent agents. It provides the pleasant sensation in mouth of the patient.

b) Durasolv Technology

Durasolv[26] is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by direct compression technique using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging systems like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

c) Wowtab technology

Wowtab technology[27] is patented by Yamanouchi pharmaceutical company. Wow means "without water". In this process, combination of low-mouldability saccharides and high mouldability-saccharides are used to obtain a rapidly melting strong tablet. Various low-mouldability saccharides are lactose, mannitol, glucose, sucrose and xylitol. Also various high-mouldability saccharides are maltose and sorbitol. A tablet prepared with low-mouldability or high-mouldability saccharides alone does not achieve adequate hardness and quick disintegration simultaneously. However if both the saccharides physically mixed before compression quick disintegration cannot be obtained. For this reason the active ingredient is mixed with a low-mouldability saccharide and granulated with a high-mouldability saccharide and compressed into tablet.

d) Flashtab technology

Flashtab technology [28] is patented by Prographarm laboratories. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug micro-granules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion-spheronization. All these processes utilized conventional tableting technology.

e) Pharmaburst technology

Pharmaburst technology is patented by SPI pharma. Tablet manufactured by this process involves a dry blend of a drug, flavour, and lubricant followed by compression into tablets; which dissolve within 30-40 seconds. Tablets manufactured by this method having sufficient strength can be packed in blister packs and bottles. [29]

f) Shearform technology

The shearform technology [27, 28] is based on preparation of floss that is also known as 'shearform matrix', which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to rapid solubilization of sugars in presence of saliva. At first, sucrose in combination with mannitol/dextrose and surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibres and also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass. Subsequently in the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head that flings the floss under centrifugal force and draws into long and thin floss fibres, which are usually amorphous in nature. The floss so produced is further chopped(conversion of fibres into smaller particles in a high shear mixer granulator) and recrystallized through an ethanol treatment(1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss. The recrystallized matrix is then blended with the drug along with other excipients and compressed into tablets. In order to improve the mechanical strength the tablets are exposed to elevated temperature and high humidity (400C and 85% RH for 15 minutes).

g) Ceform Technology

In ceform technology [29] microspheres containing active drug ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing pure drug and excipients into a rapidly spinning machine. The centrifugal force of the rotating head of ceform machine throws the dry drug blend at high speed through small heated openings. The carefully controlled temperature of the resultant microburst of heat liquefies the drug blend to form a sphere without adversely affecting drug stability. The microspheres are then blended and/or compressed into the preselected oral dosage form.

h) Ziplet Technology

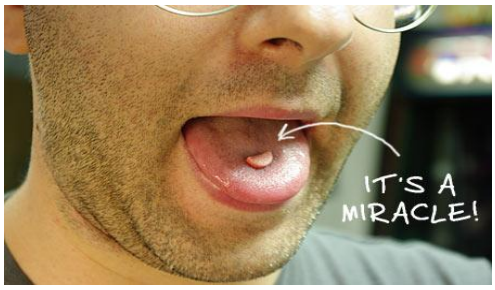
In ziplet technology water insoluble drugs or drugs as coated microparticles are used. The addition of a suitable amount of a water-insoluble inorganic excipients combined with disintegrants imparted an excellent physical resistance to the ODT and simultaneously maintained optimal disintegration.[30] The use of water-insoluble inorganic excipients offer better enhancement of disintegration in comparison to the most commonly used water soluble sugars or salts. Tablets primarily of water soluble components often tend to dissolve rather than disintegrate and concentrated viscous solution is formed which reduces the rate of water diffusion into the tablet core.[9]

i)Oraquick technology

Oraquick is a patented taste masking technology pioneered by KV pharmaceuticals. It supports the incorporation of taste masking technology. The taste masking process does not utilize solvents of any kind and therefore leads to faster and efficient production. Tablets with sufficient mechanical strength without disrupting taste masking are obtained after compression. This technology had also been utilized in the development of ODTs containing hyoscyamine sulphate which is a bitter tasting drug.[31]

j) Frosta Technology

This technology is patented by Akina. Frosta technology utilizes the core concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. The process involves mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The technology can be used for almost any drugs including aspirin, loratidine, caffeine, and folic acid, vitamins and dietary supplements. Melting time varies from several seconds to about 10 seconds depending on the formulation.



k) Nanocrystal technology

Nanocrystal technology is patented by Elan, King of Prussia. Nanocrystal ODT technology provides for pharmacokinetic benefits of orally administered nanoparticles(less than 2 microns) in the form of a rapidly disintegrating tablet matrix. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substances and water soluble ingredients filled into blister pockets. This method avoids manufacturing process such as granulation, blending and tabletting which is more advantageous for highly potent hazardous drug.

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 ODTs. 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.

i) Incorporation of sweeteners and flavors

Maximum patient acceptability with ODTs 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.[37]

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.

ii) Encapsulation or coating of drugs

Taste of 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.[38]

Various techniques utilized include

i. CIMA'S taste masking technique uses coating of drug with dissolution retarding material.[39]
ii. Phase separation approach for taste-masked microcapsules.[40]
iii. Microcaps process used microencapsulation technology.[41]
iv. Extrusion method.
v. Micromask technology used casting or spin congealing melt dispersions or solution of drug in molten blend of materials.[42]
vi. Flashtab technology.[43]
vii. Solutab technology involves coating drug with sustained release agents, which are finally coated with enteric polymers and further with mannitol.[44]
viii. Blending with cyclodextrins.[45]
ix. Coating crystals, granules, and pellets with aqueous dispersions of methacrylic acid polymers.

Precautions While Using ODTs [37]

ODTs developed offer significant advantages for various groups of patients, but the majority of patients receiving ODTs have little understanding of this novel dosage form. Patients receiving ODTs 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 ODTs. Patient information that need to be provided include:

- Storage of this dosage form as some of ODTs 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 ODTs. 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 ODTs. Some of technologies use effervescence, which experience a pleasing tingling effect on the tongue.
- Although chewable tablets are available in market and patients need to be counseled about differences between chewable and orodispersible tablets. These ODTs 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 ODTs, all patients receiving this novel dosage form could be more properly and effectively treated with greater convenience.

Conclusion

The techniques and technologies described in this article represent how recent advances in formulation development and processing technologies make the efforts to achieve orodispersible tablets. ODTs have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolve/disperse in saliva and can be administered without need of water. A number of ODT products based on various technologies are now commercially available in the international market. The basic approach followed by all the available ODTs technologies is to maximize the porous structure of tablet matrix to achieve rapid tablet disintegration in the oral cavity along with good taste-masking properties and excellent mechanical strength.

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