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An unlimited scope for novel formulations as orally disintegrating systems: Present and future prospects

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ABSTRACT

An orally disintegrating tablet or orodispersible tablet (ODT) is a drug dosage form available for a limited amount of over-the-counter (OTC) and prescription medications. ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. The ODT serves as an alternative dosage form for patients who experience dysphasia (difficulty in swallowing) or for where compliance is a known issue and therefore an easier dosage form to take ensures that medication is taken. Common among all age groups, dysphasia is observed in about 35% of the general population, as well as up to 60% of the elderly institutionalized population and 18-22% of all patients in long-term care facilities. During the last decade, ODTs have become available in a variety of therapeutic markets, both OTC and by prescription. An additional reason to use ODTs is the convenience of a tablet that can be taken without water.

Keywords: ODT, Disintegration, Dissolution test, Oral dispersible tablets

INTRODUCTION

the conventional dosage forms (tablet and capsule) have wide acceptance upto 50-60 % of the total dosage forms. Tablet is still most popular dosage form existing forms existing because of ease of self administration, compact in nature, easy to manufacture and it can be delivered in accurate dose. One drawback of solid dosage form is difficulty in swallowing (dysphasia) and chewing in some patients particularly in geriatric and paediatric patients. The problem of choking is common phenomenon in geriatric patients due to fear of choking, hand tremors, dysphasia (Habib et al ,2000). 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 rap melts. 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 (Sastry et al,2000).

Significance

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

As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients (Seager et al,1998; habib et al, 2000; Dobbetti 2003, Brown 2003).No risk of obstruction of dosage form, which is beneficial for travelling patients who do not have access to water.

Easy to administer for paediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients)

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Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action (Behnke et al, 2003).

Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavours and sweeteners in ODTs.

Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased (Jaccard et al, 1985; Dollo et al, 1999; Gafitanu et al, 1991)

Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability (Clarke et al, 2003).

Challenges to develop ODT

Rapid disintegration of tablet

Avoid increase in tablet size

Have sufficient mechanical strength

Minimum or no residue in mouth

Protection from moisture

Good package design

Compatible with taste masking technology

Not affected by drug properties

Various methods of preparation of Orodispersible Tablets

There are several methods for the preparation of orodispersible tablets but the prepared products vary in their properties depending on the method of preparation. The properties in which they vary are mechanical strength of the tablets, swallowability, bioavailability, drug dissolution in saliva, stability, and to some extent taste (Bandari et al, 2008). Various process of manufacturing of orodispersible tablets are molding, compaction, spray-drying, freeze-drying, and some special methods are melt granulation, phase transition, and sublimation.

Lyophilisation 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 lyophilisation process, which are discussed in this article. However, the ODTs formed by lyophilisation has low mechanical strength, poor stability at higher temperature, and humidity (Habib et al, 2000). along with above complications and its expensive equipment freeze-drying use is observed to be limited.

Spray Drying

Highly porous, fine powders are obtained by this method. Allen *et al*, 2001 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.

Melt granulation

It is a unique method for the preparation of orodispersible tablets by incorporating superpolystate (Allen *et al*, 1996). superpolystates are hydrophilic waxy binders with a melting point 33-37°C and hydrophilic-lipophilic balance value is 9. They play a dual role as a binder that increases the physical resistance of the tablets and also as a disintegrants, which help the tablet to melt in the mouth, and solubilize rapidly leaving no residue in the mouth. Superpolystates were introduced in the formulation of orodispersible tablets by melt-granulation method. Here, granules are formed by the molten form of this material. Crystallized paracetamol was used as a model drug along with mannitol and croscarmellose sodium.

Effervescent method

Orodispersible tablets are also prepared by effervescent method by mixing sodium bicarbonate and tartaric acid of concentration 12% (w/w) along with super disintegrants like pregelatinized starch, sodium starch glycolate, crospovidone, and croscarmellose. First, sodium bicarbonate and tartaric acid were preheated at a temperature of 80°C to remove absorbed/residual moisture and thoroughly mixed in the motor. Finally, the blends are compressed in the punch.

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 (Meyers et al, 1995) involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT. This process can accommodate high doses of drug and offers improved mechanical strength. However, high-process temperature limits the use of this process.

Approaches for taste masking

There are various drugs which do not taste good. Since orodispersible tablets dissolve in mouth, so proper taste-masking is very much essential, especially in the case of bitter taste drugs,

e.g., metronidazole (Mohire et al,2009).various approaches have been explored in order to mask the bitter or any other bad taste of the drugs which include addition of sweeteners and flavours or encapsulating the unpleasant drugs into the microparticles or by the adjustment of ph (Bandari et al,2008). In masking the bitter taste of metronidazole, Mohire *et al*, used three approaches as addition of sweetener like sodium saccharin, formation of complex and finally by numbness of the tongue. A complex was prepared by triturating drug and *glycerrhiza glabra* extract in a ratio of 1:3 in the presence of a solvent, and numbness of tongue is carried out by adding eugenol to the drug and disintegrating mixture. They found good results in the case of the complex formation of drug with *g. Glabra*. However, the most popular and general approach is the addition of sweeteners and flavours. Highly water soluble and quickly dissolvable sugar-based excipients are mannitol, aspartame, and citric acid. Flavors are mint, orange, peppermint, and strawberry. Encapsulation or coating of drugs is another method where the bad taste can be masked (Chang et al, 2000 and Morella et al, 2001).

Patented technologies for oral dispersible tablets

Zydis technology

Zydis, the best known of the fast dissolving / disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin (Gregory et al, 1981and Mizumoto et al, 1996). The product tablet is very lightweight and fragile and must be dispensed in a special blister pack .patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet .the zydis product is made to dissolve on the tongue in 2 to 3 seconds .the zydis formulation is also self preserving because the final water concentration in a freeze dried product is too low to allow for microbial growth. A major claim of zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation.

Durasolv technology :

Durasolv is cima's second generation fast dissolving / disintegrating tablet formulation. Produced in a fashion similar to orosolv, durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. Durasolv tablets are prepared by using conventional tableting equipment and have good rigidity. The durasolv product is thus produced in a faster and more cost effective manner. Durosolv is so durable that it can be packaged in traditional blister packing, pouches or vials. (Mizumoto et al, 1996 and Mizumoto et al, 2003). One disadvantage of durosolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressure on compaction.

Orosolv technology:

Orosolv was cima's first dissolving dosage form. The orosolv technology unlike zydis disperses in saliva with the aid of almost imperceptible effervescence. The orosolv technology is best described as a fast dissolving tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the orosolv formulation is twofold. The unpleasant flavour of a drug is not merely counteracted by sweeteners or flavours; both coating the drug powder and effervescence are means of taste masking in orosolv. This technology is frequently used to develop over the counter formulations (Wehling et al, 1996 and 1993).

Flash dose technology

A Fuize technology has three oral drug delivery systems that are related to fast dissolution. The first two generation of quick dissolving tablets, soft chew and ez chew, require some chewing. However, these paved the way for fuize's most recent development, flash dose technology. The flash dose technology utilizes a unique spinning mechanism to produce floss- like crystalline structure; much like cotton candy .this cryatalline sugar can then incorporate the active and be compressed into the tablet. This procedure has been patented by fuize and is known as shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue.

Flash dose tablets consist of self – binding shearform matrix termed as 'floss'. Shearform matrices are prepared by flash heat processing and are of two types (Myers et al, 1995 and Cherukuri et al, 1995).

Single floss or uniform, consisting of a carrier and two or more sugar alcohols of which one is xylitol.

Wowtab technology

The wowtab technology has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi pharmaceutical co. The wow in wow tab signifies the tablet is to be given "with out water" . It has just recently been introduced into the US. The wowtab technology utilizes sugar and sugar – like (e.g mannitol) excipients .this process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharides (good binding property) the two types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate .due to its significant hardness, the wowtab formulation is a bit more stable to the environment than the zydis and orosolv (Mizumoto et al, 1996 and 2003).

Flashtab technology

Prographarm laboratories have patented the flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the

form of microcrystal . Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion – spheronization , simple pan coating methods and microencapsulation (Cousin et al, 1995). The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets .

Oraquick technology

The oraquick fast dissolving / disintegrating tablet formulation utilizes a patented taste masking technology. Kv pharmaceutical claims its microsphere technology, known as micromask, has a superior mouthful over taste masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production .also, lower heat of production than alternative fast dissolving/disintegrating technologies makes oraquick appropriate for heat sensitive sterilization.

Patented technologies based branded products

Patented technology	Basis of technology	Technology developed by company	Active ingredient (brand name)
Zydis	Lyophilization	R.p scherer , inc	Loratidine (claritin reditab and dimetapp quick dissolve)
Durasolv	Direct compression	Cima labs , inc	Zolmitriptan (zolmig repimelt)
Orasolv	Direct compression	Cima labs , inc	Zolmitriptan (zolmig repimelt)
Flashdose	Cotton candy process	Fuize technology ltd.	Tramadol hcl (relivia flash dose)
Flashtab	Direct compression	Ethypharm	Ibuprofen (nurofen flashtab)
Wowtab	Direct compression	Yamanouchi pharma yech . Inc.	Famotidine (nurofen flastab)
Oraquick	Micromask taste masking	Kv pharm co. Inc.	Hyoscyamine sulphate mdt

Evaluation of Orodispersible tablets

Hardness/crushing strength: the hardness of the tablet is measured by using conventional hardness testers like Monsanto hardness tester (Radke et al, 2009) The limit is toward the lower range in order to help early disintegration

Friability

It is a difficult job to maintain the percentage of friability within the limit, since all the methods of preparation of orodispersible tablets have a tendency to increase the percentage of friability. In all aspect, the range is within limit of **0.1%-0.9%**.

Roche friabilator is used in conventional form in order to measure the friability of tablet.

Wetting time

Wetting time is the indication of the inner structure of the tablets and to the hydrophilicity of the excipients. Thus, wetting time of a dosage form is related with the contact angle. The lower the wetting time the quicker is the disintegration of the tablets (Bandari et al, 2008 and Radke et al, 2009). The wetting time can be measured by using five circular tissue papers of 10 cm in diameter, which are placed in a petridish of 10 cm diameter. Ten millilitres of water-soluble dye like eosin solution is added to the petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water-absorption ratio, the weight of the tablet before keeping in the petridish is noted (w_b).the wetted tablet from the petridish is taken and reweighted (w_a). The water-absorption ratio, r can be determined according to the following equation:

$$r=100(w_a-w_b)/w_b$$

Moisture uptake studies

It is an important study in the case of orodispersible tablets. This study is carried out in order to assess the stability of the tablets. Ten tablets were kept in the desiccators over calcium chloride at 37°C for 24 h. The tablets were then weighted and exposed to 75% relative humidity, at room temperature for 2 weeks (Bandari et al, 2008). Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccators for 3 days. One tablet as control (without super disintegrant) was kept to assess the moisture uptake due to other excipients.

Disintegration test

The *in-vitro* disintegration time was determined by disintegration test apparatus. The time for disintegration of orodispersible tablets is generally <1 min and actual disintegration time that patient can experience ranges from 5 to 30 s. A tablet is placed in each of the six tubes of the apparatus, and one disc is added to each tube (Swamy et al, 2008). The standard procedure of performing disintegration test for these dosage forms has several limitations. It is expected that disintegration test for orodispersible tablets should mimic disintegration in mouth within salivary contents. Sunada *et al*, 2002. Performed disintegration test by using modified United States Pharmacopoeia apparatus II by taking 900 ml of medium maintaining 37°C with r/min 100. It was carried out by taking a 1 l cylindrical vessel. Orodispersible tablets were placed in basket sinker in the middle of the vessel with a distance of 6-8.5 cm. even Narazaki *et al*, 2004, Carried out the disintegration test with rotary-shaft method. The apparatus consisted of stainless steel wire gauze on which orodispersible tablets were placed and slightly immersed in medium. Here, the

rotary shaft is used to provide rotation and mechanical stress.

Dissolution test

It is an important test as the drug-release profile can be obtained by performing this test. Both the usp dissolution test apparatus can be used. Dissolution of orodispersible tablets is very fast. Therefore, USP 2 paddle-type apparatus at 50-100 r/min is used for dissolution testing. Swamy *et al.* carried out *in vitro* dissolution study of pheniramine maleate orodispersible tablets in type ii apparatus with r/min 550 using 900 ml phosphate buffer of ph 6.8 at $37 \pm 0.5^\circ\text{C}$ as dissolution medium (Narazaki *et al.*, 2004). Usp type i basket apparatus have certain application in the case of orodispersible tablets, but tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle. An erroneous-dissolution profile is obtained, where little or no effective stirring occurs. Thus, type ii is more preferred due to reproducible-dissolution profile.

Conclusion:

ODT concept evolved to overcome some of the problems that existed in conventional solid dosage form i.e. difficulty in swallowing of tablet in pediatric and geriatric patients who constitute a large proportion of world's population. ODT may lead to improve efficacy, bioavailability, rapid onset of action, better patient compliance due to its quick absorption from mouth to GIT as the saliva passes. Fast dissolving tablet acts like solid dosage form when outside the body and solution when administered. In future ODT may be most acceptable and prescribed dosage form due to its quick action (within minute). Their characteristic advantages such as administration without water, anywhere, anytime lead to their increased patient compliance in today's scenario of hectic life. Considering the many benefits of ODTs, a number of formulations are prepared in ODT forms by most of the pharmaceutical companies. Because of increased patient demand, popularity of these dosage forms will surely expand in future.

Table:2 ODTs currently or previously available

Product	Manufactured by/for	Active ingredient	Category	Indication	Intended age group
Abilify discmel	Otsuka america/bristol-myers squib	Aripiprazole	Atypical antipsychotics	Schizophrenia, bipolar disorder, adjunct therapy for major depressive disorder	13 years+ for schizophrenia, 10 years+ for bipolar disorder, adults for md
Alavert quick dissolving tablets	Wyeth	Loratadine	Anti-histamines	Allergy	6 years +
Allegra odt	Sanofi aventis	Fexofenadine	Anti-histamines	Allergic rhinitis, urticaria	6-11 years
Aricept odt	Eisai co.	Donepezil	Acetylcholinesterase inhibitors	Alzheimer's disease ¹	Adults
Benadryl fastmelt	Pfizer	Diphenhydramine	Anti-histamines	Allergy	6 years+
Calpol fast melts	Mcneil healthcare uk	Paracetamol	Analgesics	Pain	6 years+
Clarinetax reditabs	Schering-plough	Desloratadine	Anti-histamines	Allergy	6 years+
Claritin reditabs	Schering-plough	Loratadine	Anti-histamines	Allergy	6 years+
Clonazepam odt	Par pharmaceutical	Clonazepam	Benzodiazepines	Anxiety, panic disorder, seizure disorders	Infants+
Fazaclo	Azurpharma	Clozapine	Antipsychotics	Treatment-resistant schizophrenia	Adults
Jr. Tylenol meltaways	Mcneil consumer healthcare	Acetaminophen	Analgesics, antipyretics	Pain, fever	6 years+
Klonopin wafers	Roche	Clonazepam	Benzodiazepines	Panic disorder, seizure disorders	Infants+ for seizure disorders, adults for panic disorder
Loratadine redidose	Ranbaxy	Loratadine	Antihistamines	Allergy	6 years+
Mirtazapine odt	Teva pharmaceuticals	Mirtazapine	Antidepressants	Major depressive disorder ¹	Adults
Niravam	Schwarz pharma	Alprazolam	Benzodiazepines	Anxiety, panic disorder	Adults 18+

Ondansetron odt	Teva pharmaceuticals	Ondansetron	Antiemetics	Nausea, vomiting	4 years+
Parcopa	Schwarz pharma	Carbidopa/levodopa	Ddc inhibitors [carbidopa]	Parkinson's disease	Adults
Prevacid solutab	Takeda pharmaceuticals	Lansoprazole	Proton pump inhibitors	Gastro-oesophageal reflux disease (gerd),	1 year+
Remeron soltab	Schering-plough	Mirtazapine	Antidepressants	Major depressive disorder	Adults
Risperdal m-tab	Janssen	Risperidone	Atypical antipsychotics	Schizophrenia, bipolar disorder, irritability associated with autistic	13 years+ for schizophrenia, 10 years+ for bipolar disorder, 5 years+ for autism
Zelapar	Valeant pharmaceuticals int'l	Selegiline	Monoamine oxidase inhibitors (maois)	Adjunct therapy in parkinson's disease	Adults
Zyprexa zydis	Eli lilly and company	Olanzapine	Atypical antipsychotics	Bipolar disorder, schizophrenia	Adults

Table:3 ODTs under development

Product	Manufacturer	Active ingredient	Category	Indication	Intended age group
Citalopram odt	Biovail	Citalopram	Ssis	Major depressive disorder	
Metoclopramide zydis	Salix pharmaceuticals	Metoclopramide	Dopamine receptor antagonists	Short-term therapy for gerd, acute diabetic gastric stasis	Adults
Reglan odt	Schwarz pharma	Metoclopramide	Dopamine receptor antagonists	Short-term therapy for gerd, acute diabetic gastric stasis	Adults
Tramadol/acetaminophen odt	Biovail	Tramadol/acetaminophen	Opioid analgesic [tramadol]	Pain	Adults
Zolpidem odt	Biovail	Zolpidem	Nonbenzodiazepine hypnotics	Sleep disorders	Adults

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