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Design and Novel Approaches of Orally Disintegrating Tablets

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Abstract

Tablets designed to dissolve on the buccal (cheek) mucous membrane were a precursor to the ODT. This dosage form was intended for drugs that yield low bioavailability through the digestive tract but are inconvenient to administer parenterally, such as steroids and narcotic analgesics. Absorption through the cheek allows the drug to bypass the digestive tract for rapid systemic distribution. Not all ODTs have buccal absorption and many have similar absorption and bioavailability to standard oral dosage forms with the primary route remaining GI absorption. However, a fast disintegration time and a small tablet weight can enhance absorption in the buccal area. The first ODTs disintegrated through effervescence rather than dissolution, and were designed to make taking vitamins more pleasant for children. This method was adapted to pharmaceutical use with the invention of microparticles containing a drug, which would be released upon effervescence of the tablet and swallowed by the patient.

Keywords: Tablets, Zydis ODT, Claritin.

Contents

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1. Introduction

An orally disintegrating tablet or or dispersible tablet (ODT) is a drug dosage form available for a limited range of over-the-counter (OTC) and prescriptionmedications. 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 dysphagia (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, dysphagia 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 an ODTs is the convenience of a tablet that can be taken without water.ODTs offer numerous significant advantages over conventional dosage forms because of improved efficacy, bioavailability, rapid onset of action, better patient compliance, and acceptance. Pediatric and geriatric patients are primary concerns, as both the groups find these dosage forms convenient to administer as compared to the conventional dosage forms. ODTs can be prepared in

several ways and product performance depends upon the drug suitability and excipients selection in the delivery system. Due to the availability of various formulation techniques, good patient compliance and huge potential, several products have already been commercialized.Furthermore, market size and popularity of these dosage forms will surely expand in future. It is also emphasized that newer with continued development of new pharmaceutical scientific and technological innovations should be undertaken for the emergence of promising and versatile dosage form with novel performance and characteristics for ODTs in days to come.

Historical Development

Tablets designed to dissolve on the buccal (cheek) mucous membrane were a precursor to the ODT. This dosage form was intended for drugs that yield low bioavailability through the digestive tract but are inconvenient to administer parenterally, such as steroids and narcotic analgesics. Absorption through the cheek allows the drug to bypass the digestive tract for rapid systemic distribution. Not all ODTs have buccal absorption and many have similar absorption and bioavailability to standard oral dosage forms with the primary route remaining GI absorption. However, a fast disintegration time and a small tablet weight can enhance absorption in the buccal area. The first ODTs disintegrated through effervescence rather than dissolution, and were designed to make taking vitamins more pleasant for children.

This method was adapted to pharmaceutical use with the invention of microparticles containing a drug, which would be released upon effervescence of the tablet and swallowed by the patient. Dissolution became more effective than effervescence through improved manufacturing processes and ingredients (such as the addition of mannitol to increase binding and decrease dissolution time).CatalentPharma Solutions (formerly Scherer DDS) in the U.K., Cima Labs in the U.S. and Takeda Pharmaceutical Company in Japan led the development of ODTs.The first ODT form of a drug to get approval from the U.S. Food and Drug Administration (FDA) was a Zydis ODT formation of Claritin (loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (clonazepam) in December 1997, and a Zydis ODT formulation of Maxalt (rizatriptan) in June 1998. The regulatory condition for meeting the definition of an orally disintegrating tablet is USP method 701 for Disintegration. FDA guidance issued in Dec 2008 is that ODT drugs should disintegrate in less than 30 seconds. This practice is under review by the FDA as the fast disintegration time of ODTs makes the Disintegration test too rigorous for some of the ODT formulations that are commercially available.

2. Description

Ideal Properties of ODTS:

The performance of ODTs depends on the manufacturing technology and the most necessaryproperty of such a dosage form is the ability of rapidly disintegrating and dispersing or dissolving in the saliva, thereby obviating the need for water intake. ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms are:

i. Convenient and easy to administer as does not require water for oral administration for swallowing purpose, but it should dissolve or disintegrate in the mouth usually within few seconds.
ii. Allow high drug loading.
iii. Provide pleasant feeling in the mouth.
iv. Be compatible with taste masking and other excipients.
v. Leave negligible or no residue in the mouth after
vi. Have sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling.
vii. Insensitive to environmental conditions such as humidity and temperature.
viii. Adaptable and amenable to conventional processing and packaging equipments at nominal expense.

Advantages of ODTS:

Advantages of ODTs include:

i. Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
ii. ii. The ODTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.
iii. Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.
iv. Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus. Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.
v. Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.
vi. Good mouth feels, especially for pediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.

vii. Minimum risk of suffocation in airways due to physical obstruction, when ODTs are swallowed, thus they provide improved safety and compliance with their administrations.
viii. Rapid drug therapy intervention is possible.
ix. Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

Formulating ODTS:

The processes used to manufacture orally disintegrating tablets include loose compression tabletting, a process which is not very different than the manufacturing method used for traditional tablets and lyophilization processes. In loose compression, ODTs are compressed at much lower forces (4 – 20 kN) than traditional tablets. However, since ODTs are compressed at very low forces due to the need to them to be soft enough to disintegrate rapidly in the mouth, issues of material sticking to the die walls can be challenging. Typically, as in most tablet blends, lubricants such as magnesium stearate are added to the blend to reduce the amount of material that may stick to the die wall. Differences may be the use of disintegrating aids, such as crospovidone, and binding agents that aid in mouth feel, such as microcrystalline cellulose. Primarily, ODTs contain some form of sugar such as mannitol, which typically serves as the major diluent of the ODTs, and is also the primary contributor to the smooth and creamy mouth feel of most ODTs. Lyophilized ODT formulations may use proprietary technologies but can produce a tablet that has a faster disintegration rate, for example the Zydis ODT typically dissolves in the mouth in less than 5 seconds without water.Super disintegrants in direct compression process have greater direct impact on rate of disintegration and dissolution of tablets. The presence of other formulation ingredients such as water- soluble excipients and effervescent agents further hastens the process of disintegration. Microcrystalline cellulose (MCC) and low substituted hydroxyl propyl cellulose (HPC) can alsobe used to manufacture ODT. The ratio of MCC to HPC varied from 8:2 to 9:1. agar powder can also be used as a disintegrant because the powder absorbs water and swells without forming gel at physiological temperature. Ethypharm (France) has introduced a Flash- dose technology, which contains coated crystals and micro granules along with the disintegrants. In this technology, two types of granules are used; a disintegrating agent (e.g. modified cellulose- Croscarmellose) which has a high swelling force, and a swelling agent (e.g. starch) which has a low swelling force. tablets by dry granulation method using three super disintegrants, Croscarmellose sodium (Ac-Di-Sol), Crosspovidone and Sodium starch glycolate and they found that Ac-Di-Sol was the best super disintegrant among the three.

Manufacturing Technology

1.OraSolv

The ideal orally disintegrating tablet formulation disintegrates quickly in the oral cavity, releases 100% of the active ingredient in the gastrointestinal tract, and has a pleasant taste and creamy mouth feel. The fast disintegration is achieved by compressing water-soluble excipients using a lower range of compression forces than are normally used in tableting. The time for the disintegration of OraSolv tablets within the oral cavity varies from 6 s to 40 s, depending largely on tablet size and the compression force (within the lower range) that was used to form the tablet. The low compression force leads to high tablet porosity which, in turn, accelerates the rate of disintegration of the tablet and dissolution of the water-soluble excipients. Disintegrating agents further facilitate the process, an effervescent couple being used as a water-soluble disintegrating agent . Thus, the OraSolv tablet comprises the components: taste-masked active(s), filler, sweetener, disintegrating agent, lubricant, glidant, flavor, and coloring agent. The active ingredients can be taste-masked using a variety of techniques.

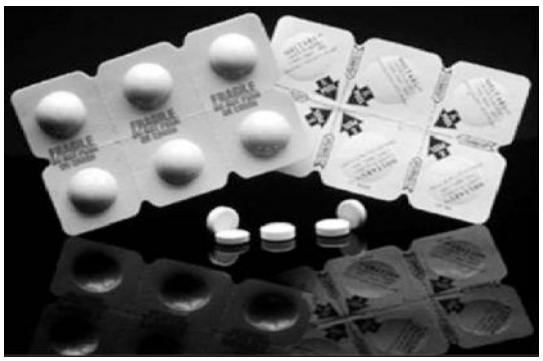

Fig.1:Orasolv and Durasolv tablets

2.DuraSolv

DuraSolv is Cima's second-generation fast-dissolving tablet technology. This technology provides robust yet quick-dissolving tablets. Like OraSolv, the Dura-Solv tablets consist of water-soluble excipients and are manufactured using direct compression techniques. However, DuraSolv utilizes nondirectly compressible fillers in fine particle form [6,7]. These fillers have a high surface area, which increases their dissolution rate. The incorporation of a high proportion of such fillers causes the tablet to "melt" or dissolve, rather than disintegrate. Wicking agents assist the

entry of water into the body of the tablet, whereas swelling disintegrants are avoided or used in small proportions. Since extensive disintegration is to be avoided, only small amounts of effervescent agents may be incorporated, if they are to be included at all. The limited disintegration contributes to the nongritty mouth feel conferred on the product by the use of fine-particle fillers. The increased dissolution rate of the soluble, fine-particle filler compensatesfor the reduction in tablet porosity due to the use of higher compression forces (relative to the OraSolv products). The manufacturing process utilizes conventional blenders and high-speed tablet presses. DuraSolv tablets are robust and conventional packaging equipment can be used to package theminto bottles. The product may also be packaged into blisters or pouches, if desired.

3.OraQuick technology (KV Pharmaceutical Co.Inc.):

OraQuick utilizes its own patented taste masking technology i.e. MicroMask®. In MicroMask® technology,taste-masking process is done by incorporating drug into matrix microsphere. In this technique, tablet is prepared by dissolving the sugar (sucrose, mannitol, sorbitol, xylose, dextrose, fructose, or mannose) and protein (albumin or gelatin) in a suitable solvent such as water, ethanol, isoproryl alcohol and ethanol-water mixture. The solution of matrix is then spray dried, yielding highly porous granules. In addition, utilization of lower heat of production is advantageous for heat-sensitive drugs. Granules formed then mixed with drug and other excipients and compressed at low compression force. KV pharmaceuticals claimed that matrix formed protects and surrounds the drug powder in microencapsulated particles is more reliable during this step.

4.Multiflash technology (Prographarm): Multiflash is a multi-unit tablet composed of coated microgranules and fast-disintegrating excipients. This multiparticulate tablet quickly disintegrates in the esophagus after being swallowed with a minimum amount of water. This tablet avoids mucosal adhesion, and coated pellets can match various dissolution rates.

5.Lyoc:

Lyoc is a porous and solid galenic form obtained by lyophilization of an oil-in-water emulsion placed directly in the blister alveolus.[39] The method of preparation involves freezing a thickened (paste-like) emulsion containing the active as bulk or as coated microparticles. This product is capable of accommodating high dose and disintegrates rapidly but possesses poor mechanical strength

ODTs currently or previously available

Product	**Manufactured By/For**	**Active ingredient**	**Category**
Abilify Discmelt	Otsuka America/Bristol-Myers Squibb	Aripiprazole	Atypical antipsychotics
Alavert Quick Dissolving Tablets	Wyeth	Loratadine	Anti-histamines
Allegra ODT	Sanofi Aventis	Fexofenadine	Anti-histamines
Aricept ODT	Eisai Co.	Donepezil	Acetylcholinesterase inhibitors[2]
Benadryl FastMelt	Pfizer	Diphenhydramine	Anti-histamines
Calpol Fast Melts	McNeil Healthcare UK	Paracetamol	Analgesics
ClarinexRediTabs	Schering-Plough	Desloratadine	Anti-histamines
Claritin RediTabs	Schering-Plough	Loratadine	Anti-histamines
Clonazepam ODT	Par Pharmaceutical	Clonazepam	Benzodiazepines
Edluar	Meda AB	Zolpidem	NonbenzodiazepineHypnotics
FazaClo	AzurPharma	Clozapine	Antipsychotics
Fluimucil	AlpexPharma SA / Zambon Group	N-Acetylcysteine	Mucolitic
Jr. Tylenol Meltaways	McNeil Consumer Healthcare	acetaminophen	Analgesics, Anti-pyretics
Klonopin Wafers[27]	Roche	clonazepam	Benzodiazepines
Lamictal ODT	Aptalis /GlaxoSmithKline	lamotrigine	Anticonvulsant
LoratadineRedidose	Ranbaxy	loratadine	Antihistamines
Maxalt-MLT	Merck & Co.	Rizatriptan	Triptans/Serotoninagonists

Future Directions

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

3. Conclusion

An orally disintegrating tablet or orodispersible tablet (ODT) is a drug dosage form available for a limited range of over-the-counter (OTC) and prescription medications. ODTs offer numerous significant advantages over conventional dosage forms because of improved efficacy, bioavailability, and rapid onset of action, better patient compliance, and acceptance. For new technologies that provide significant clinical as well as financial value, research and innovation in the contract manufacturing and pharmaceutical segments lead to the emergence of numerous competing versions of the technologies. Such a technology evolution has been evident for orally disintegrating tablets (ODTs). Designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing, these formulations offer increased convenience and ease of administration with the potential to improve compliance, particularly in certain populations where swallowing conventional solid oral-dosage forms presents difficulties.

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