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Mouth dissolving tablet: Superdisintegrants and technology used: An overview

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ABSTRACT

The tablet is most widely used dosage form because of its convenience in terms of self administration, compactness, and ease of manufacturing. There is a demand for more patient – friendly and compliant dosage forms. As a result the demand for developing new technologies has been increasing annually. Mouth dissolving tablets are ideal for many groups of patients including geriatrics, pediatrics, psychiatrics and for those people who have difficulty in swallowing. By using such manufacturing technologies, many drugs can be formulated in the form of mouth dissolving tablets to provide the advantage of liquid medication in the form of solid preparation One such problem can be solved in the novel drug delivery system by formulating "mouth dissolving tablets"(MDTs) which disintegrates or dissolves rapidly without water within a few seconds in the mouth due to the action of superdisintegrant or maximizing pore structure in the formulation. The present study illustrates various technologies and excipients used in mouth dissolving tablets.

Keywords: Geriatric, Novel drug delivery system, Pediatric, Superdisintegrant.

1. INTRODUCTION

The MDTs should not have a bitter taste and should have low dose of drug (about 20 mg). Drug molecular weight should be small to moderate and good stability in water and saliva. It should be partially non – ionized in the oral cavities pH and have ability to diffuse and partition into the epithelium of the upper GIT [1].

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. A wide range of emulsifiers are recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated into the range of 0.05 percent to about 15 percent by weight of the final composition. Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients [2,6,7].

Fast mouth dissolving tablets (MDTs) are also known as fast dissolving, rapid melt, fast melt, orodispersible, melt-in-mouth, quick dissolving porous tablets or effervescent drug absorption system [1]. According to European pharmacopoeia, these MDTs should dissolve or disintegrate in less than three minutes [2]. The formulation is more useful for bedridden patients who have the swallowing problem [2,4]. However, of all the above terms united states pharmacopoeia (USP) approved these dosage forms as Oral dispersible tablets (ODTs). United States food and drug administration (FDA) defined ODTs as "A solid dosage form when placed upon the tongue"[2, 3].

The aim of the present review is to study the feasibility of fast mouth dissolving drug delivery and background of superdisintegrants and technologies used for MDT [3].

1.1. Superdisintegrants

A Superdisintegrant is an excipient, which is added to a tablet or capsule blends to aid in the breakup of the compacted mass when it is put into a fluid environment. various superdisintegrants and their mechanism given in table 1.

The tablet breaks into primary particles of one or more of the mechanisms listed below:

Disintegration by capillary action is always the first step. When we put the tablet in suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on

Table -1: Some of existing Superdisintegrants and their mechanism of action [13,14]

Name of the disintegrant	Brand name	Concentration (%)	Mechanism of action
Sodium starch glycolate	Explotab, Primogel	2-8%	Swelling
Micro crystalline cellulose	Avicel, celex	2-15%	Water wicking
Cross linked povidone	Cross povidone	2-5%	Swelling,water wicking
Low substitute hydroxyl propyl cellulose	LH-11,LH-12(Grades)	1-5%	Swelling
Crosscarmellose sodium	Ac-Di-Sol	13%Directcompression 2-4% wet granulation	Wicking and swelling
Pregelatinized starch	Starch 1500	1-20%	Swelling

Table -2: Drugs promising to be incorporated in MDTs [10,11]

Category	Drugs
Analgesics and anti inflammatory agents	Aloxiprin, Auranofin, Azapropazone, Etodolac, Fenbufen, Flubiprofen, Indomethacin, Ketoprofen, Mefanamic acid, Nabumetone, Naproxen, Oxaproxen, phenylbutazone, Piroxicam,
Anthelmintics	Albendazole, Bepheniumhydroxy napthoate, Cambendazole, Mebendazole
Antibacterial agents	Benethamine penicillin, Ciprofloxacin HCL, Clofazimine, Demeclocycline, doxycycline, Erythromycin,
Anticoagulants	Dicoumarol, dipyridamole, nicoumalone, phenindione
Antidepressants	Amoxapine, Ciclazindol, Maprotiline HCL, Nortriptyline HCL, Trazodone HCL, Trimipramine maleate
Anti epileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin,Methoin, Methosuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone
Anti hypertensive agents	Amlodipine, Carvedilol, Benidipine, Darodipine, Diazoxide, Felodipine, Nicardipine, Isradipine
Anti – Diabetics	Acetohexamide, Chlorpropamide, Glibenclamide, Glipizide, Tolazamide, Tolbutamide
Anti migraine agents	Dihydroergotamine mesylate, Ergotamine tartrate, Sumatriptan, Rizatriptanbenzoate, Zolmitriptan
Antipsychotics	Clozaril, Fanapt, Fluphenazine,Clozapine, Haloperidol, loxitane, Paliperidone, loxapine.

the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions.

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. When disintegrates with exothermic properties gets wet, localized stress is generated due to capillary air expansion, which helps in the disintegration of the tablet. This explanation, however, is limited to only a few types of disintegrates and cannot describe the action of most modern disintegrating agents.

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. As these disintegrates are highly sensitive to small changes in humidity level and temperature, strict control of the environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added into two separate fractions of formulation.

Table -3: Some marketed mouth dissolving tablets [13,14]

Brand name	Drug	Pharmaceutical company
Benadryl Fastmelt	Diphenhydramine	Pfizer
Benadryl Fast melt	Diphenhydramine	Warner Lambert
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Domray MD	Domperidone	Ray Remedies
Dolib MD	Rofecoxib	Panacea
Feldene melt	Piroxicam	Pfizer
Febrectol	Paracetamol	Prographarm
Imodium Instant melts	Loperamide Hcl	Janssen
Kemstro	Baclofen	Schwarz Pharma
Klonopin Wafers	Clonaxepam	Roche
Maxalt-MLT	Rizatriptan Benzoate	Merck
Mosid MT	Mosapride	Torrent
Nulev	Hyoscyamine sulfate	Schwarz Pharma
Nimulid MD	Nimusulide	Panacea
Orthoref MD	Rofecoxib	Biochem
Olanex Instab	Olanzepine	Ranbaxy
Pepcid ODT	Famotidine	Merck
Rofaday MT	Rofecoxib	Lupin
Torrox MT	Rofecoxib	Torrent
Valus	Valdecoxib	Glenmark
Zotacet MD	Cetrizine Hcl	Zota Pharma
Zyprexa	Olanzapine	Eli lilly

Here, enzymes present in the body act as disintegrant. These enzymes destroy the binding action of the binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Another mechanism of disintegration attempts to explain the swelling of tablets made with 'non-swellable' disintegrates. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also causes disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Occasionally, the swelling capacity of starch was proved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and recently begin to be studied [2,13,14].

Some drugs can be incorporated as mouth dissolving tablets and some tablets are already marketed, it has been listed in table 2 and 3.

1.2. Technologies used for the fast mouth dissolving tablet preparation.

1.2.1. Non patented technologies [2 ,6 -8, 20]

1.2.1.1. Melt granulation

This technique is a process by which pharmaceutical powders are efficiently agglomerated by a metal binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents are needed. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

1.2.1.2. Phase transition

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making MDTs without any special

apparatus. MDT was produced by compressing powder containing erythritol (melting point: 122 °C) and Xylitol (melting point: 93 95 °C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased.

1.2.1.3. Sublimation

In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

1.2.1.4. Mass extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which is finally cut into even segments using a heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste.

1.2.1.5. Spray drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone are used as superdisintegrants. A tablet manufactured from the spray-dried powder has been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose.

1.2.1.6. Direct compression

Direct compression represents the simplest an most cost effective tablet manufacturing technique. This technique can now be applied to the preparation of MDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

1.2.1.7. Freeze drying or lyophilization

The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze- drying. Finally the blisters are packaged and shipped.

1.2.1.8. Fast dissolving films

A non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyl ethyl cellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film.

1.2.2. Patented technologies [12,13,15,19]

1.2.2.1. Zydis

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and 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. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

1.2.2.2. Orasolv

Orasolv Technology has been developed by "CIMA" labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

1.2.2.3. Durasolv

This too has been developed by CIMA labs. This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tabletting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid. Dosage form can be packaged into conventional packaging system like blisters.

1.2.2.4. Flash dose

This technology is patented by Fuisz. This system uses the combination of both Shearform and Ceform technologies in order to mask the bitter taste of the drug. A sugar based matrix, called 'Floss' is used, which is made up of a combination of excipients (crystalline sugars) alone or in combination with drugs. Nurofen meltlet, a new form of Ibuprofen, as a mouth-dissolving tablet is the first commercial product prepared by this technology and launched by Biovail Corporation.

1.2.2.5. Flash tab

Prographarm laboratories have patented the flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tableting technology.

1.2.2.6. Wowtab

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (eg. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (eg. Maltose, oligosaccharides) and compressed into table.

1.2.2.7. Nanocrystal

For MDT, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics.

Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug For fast dissolving tablets, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology.

NanoCrystal Fast dissolving technology provides for:

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix.
- Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters).
- Wide range of doses (up to 200mg of API per unit).
- Employment of non moisture sensitive substances.

2. CONCLUSION

MDTs concept evolved to overcome some of the problems that existed in conventional dosage form i.e. difficulty in swallowing of tablet. Superdisintegrants and various technologies are used mainly to make MDT successful. The present study is highly concise and illustrative to describe about MDT, which 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. MDTs characteristics and advantages such as administration without water, anywhere, anytime lead to their increased patient compliance in todays hectic life. Considering the many benefits of MDTs, a number of formulations are prepared in MDT forms by many pharmaceutical companies. Because of increased patient demand, popularity of these dosage forms will surely expand in future.

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