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A review - Formulation and evaluation of mouth dissolving tablets

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ABSTRACT

Fast dissolving drug delivery system was an advanced system; oral tablet administration to patient was a significant problem and has become the object or fast dissolving oral forms, which do not require water to aid swallowing. The dosage forms dissolve or disintegrate in oral cavity within a minute. This review presents view of the criteria, Salient features, advantages, and limitation, formulation aspects in developing fast dissolving tablets, various approaches, various technologies involved and evaluation parameters of fast dissolving tablets.

Keywords: Fast dissolving tablet, patented technologies, Conventional technologies, Evaluation of FDTs.

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via various pharmaceutical products of different dosage forms [1-22]. The reason that the oral route achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food staffs ingested daily. In fact the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form within the inherent constraints of GI physiology. Therefore a fundamental understanding of various disciplines, including GI physiology Pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral dosage form. The more sophisticated a delivery system the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case the scientific development of oral drug delivery system consists of a basic understanding of the following there aspects.

- Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
- The anatomic and physiologic characteristic of the GIT.
- Physicochemical characteristic and the drug delivery mode of the dosage form to be designed.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules. Drinking water plays an important role in the swallowing of oral dosage forms. One important drawback of these dosage forms for some patients however is difficulty to swallow. Often times people experience inconvenience in swallowing conventional tablets and capsules when water is not available in case of motion sickness and sudden episodes of coughing during the common cold, allergic conditions and bronchitis.

Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed[8]. It is estimated that 50% of the population is affected by this problem which results in a high incidence of non compliance and in effective therapy. It has been reported that dysphasia (difficulty in swallowing) is common among all age groups and more specific with

pediatric, geriatric population along with institutionalized patients and patients with nausea [8]. Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way.

The orally disintegrating tablets are also caused as orodispersible tablet, quick disintegrating tablets, fast disintegrating tablets, porous tablets rapimelts. However of all the above terms, United States pharmacopeia (USP) approved these dosage forms as ODTs. Recently, European pharmacopeia has used the term "orodispersible tablet" for tablets that disperse readily and within three minutes before swallowing. 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" [8]. The disintegration time for ODTs generally ranges from several seconds to about a minute.

Mouth dissolving tablets are most widely used dosage form because of it's convenience in terms of self administration, compactness and ease in manufacturing. Fast disintegrating tablets rapidly gaining acceptance as an important new drug technology. These dosage forms dissolve or disintegrate in oral cavity within a minute even without the need of water or chewing [2].

1.1. Desired criteria for mouth dissolving drug delivery system [9, 22]

The tablet should:

- Not require water to swallow, but is should dissolve (or) disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable with taste masking.
- Have a pleasing mouth feel.
- Leave minimal (or) no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allow the manufacture of tablet using conventional processing and packaging equipment at low cost,
- Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

1.2. Salient features of mouth dissolving tablet [3,8,11]

- Ease of administration to patient who refuses to swallow tablets, such as pediatric, geriatric and psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- Rapid dissolution and absorption of drug which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach in such cases bio-availability of drugs in increased.
- Pre-gastric absorption can result in improved bio-availability and as a result of reduced dosage. Improve clinical performance through a reduction of unwanted effects.

1.3. Advantages of mouth dissolving tablets [1,3,11]

- Improved patient compliance.
- Rapid onset of action and may offer an improved bio-availability.
- Patient having difficulty in swallowing tablet can easily administer this type of dosage form.
- Useful fro-pediatric, geriatric and psychiatric patients.
- Suitable during travelling where water is may not be available.
- Gives accurate dosing as compared to liquids.
- Good chemical stability.
- Free of need of measuring, an essential drawback in liquids.

1.4. Limitation of mouth dissolving tablets[13]

- The tablets usually have insufficient mechanical strength. Hence careful handling is required.
- The tablets may leave unpleasant taste and for grittiness in mouth if not formulated properly.

- These tablets usually have low hardness, so they are friable or brittle. They are difficult to handle.
- And require specialized packaging.

1.5. Significance of dissolving tablets

- They provide good stability, accurate dosing, and easy manufacturing small packaging size and easy to handle by patients.
- No risk of obstruction of dosage from, which is beneficial for travelling patients who do not have access to water.
- Easy to administer for pediatric, geriatric and institutionalized patients. (especially for mentally retarded and psychiatric patients)
- Rapid disintegration of the tablet results in quick dissolution and rapid absorption which provide rapid onset of action.
- Medications as "bitter pill" has changed by excellent mouth feel property produced by the use of flavors and sweeteners in mouth dissolving tablets.
- Bioavailability of drugs that are absorbed from mouth, pharynx and oesophagus is increased.
- Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.
- Improved taste and not produce any residue in the mouth.
- Insensitive to environmental conditions.

1.6. Formulation aspects in developing MDT

Mouth disintegrating tablets are formulated by utilizing several process, which differ in their methodologies and the MDTs formed vary in various properties such as,

- Mechanical strength of tablets
- Taste and mouth feel
- Swallowability
- Drug dissolution in saliva.
- Bioavailability
- Stability

1.7. Various approaches for mouth dissolving tablets [16]

The property of mouth dissolving tablets is attributable to a quick intake of water in to the tablet matrix resulting rapid disintegration and instantaneous dissolution of the tablets.

- Maximizing the pore structure of tablet matrix.
- Using highly water soluble excipients in the formulation.
- Incorporating appropriate disintegrating agents.

Disintegrates act by any one of the following mechanisms,

- Capillary action
- High swell ability
- Release of gas by chemical reaction.

1.8. Methods for the formulation of mouth dissolving tablets[15]

Various processes employed in formulating MDTs are described below.

1.8.1. Patented technologies [4,8]

Zydus technology

This technology involves physical trapping of drug in a matrix composed of a saccharide and a polymer[8] .The polymer generally used are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginate, polyvinyl alcohol, polyvinyl pyrrolidone, 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 is used to pack zydis units. These formulations are sensitive to moisture and may degrade at humidity greater than 65% zydis is patented by R.P. Scherer.

Lyoc

Oil in water emulsion is prepared and placed directly in to blister cavities followed by freeze drying. Non homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. The methodology is patented by pharmalyoc [8].

Quick Solv

Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess alcohol (solvent extraction). The product formed has uniform porosity and adequate strength for handling. This technology patented by Jassen Pharmaceuticals [8].

Nanocrystal technology

Nanocrystal technology includes lyophilization of colloidal dispersion of drug and water soluble ingredients filled into blister pockets. This method avoids manufacturing

process such as granulation, blending and tableting. This method is advantageous for highly potent and hazards drugs. Manufacturing losses are negligible and the process is small quantities of drugs. This methodology is patented by Elan,king of Prussia.

Flash tab technology

This technology includes granulation of excipients by wet granulation method and follow by compressing in to tablets exicipients used in this technology are of two types. Disintegrating agents include reticulated polyvinyl pyrolidone or carboxy methyl cellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. tablets formed have satisfactory physical resistance. disintegrance time is within one minute. This methodology patented by Ethypharm, france.

Orasolv tecnology

This includes use of effervescent disintegrating agents compressed with low pressure to produce MDTs. The evaluation of carbon dioxide from the tablet produce fizzing sensation, which is a positive organoleptic properties. Concentration of effervescent mixed usually employed is 20-25% of tablet weight .as the tablets prepared at low compression force, they are soft and fragile in nature. This is initiated to develop paksolv, a special packaging to protect tablets during storage and transport. Paksolv is dome-shaped blister package, which prevents vertical movements of tablets in the depression. This offers moisture, light and child resistance packing.

Durasolv tecnology

This methodology utilized conventional tableting equipment and tablets are formulated by using drug nondirect compression fillers and lubricants.non direct compression fillers are dextrose mannitol, sorbitol, lactose, and sucrose which have advantages of quick dissolution avoid gritty structure (which is generally present in direct compressible sugar)The tablets formed are strong and can be packed in conventional packing in bottles and blisters. nondirect compressible fillers generally used in the range of 60-95%,lubricants in 1-2.5%.this technology patented by CIMA labs[8]. Durasolv products include Nulev (hyoscyaminesulphate), Zoming ZMT(Zolmitraptan).

Wow tab tecnology

This technology utilizes conventional granulation and tableting methods to produce MDTs employing low-and high moldability saccharides. WOW means without water[8]. Low moldabilty saccharides are lactose, mannitol, glucose, sucrose, and xylitol. high moldability saccharides are maltose, maltitol, sorbitol and oligosaccharides. When these two type saccharides used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combilnation are used. This technology involves granulation of low-moldable saccharieds as abinder and compressing in to tablets followed by moisture treatment. So the tablets formed showed adequate hardness and rapid disintegration. This technology patented by Yamanouchi[8].WOW tab product include Benadryl allergy and sinus fast melt (OTC)

Dispersible tablet tecnology

It offers devolepment of MDT improved dissolution rate by incorporating 8-10% of organic acid and disintegrating agents. disintegrating agents facilitates rapid swelling and good wetting results in quick disintegration. Disintagrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross linked sodium carboxy methyl cellulose and cyclodextrines. Combilnation of disintegarants improved disintegration usally less than 1 minutes. The methodology patented lek, Yugoslavia.

Pharma burst technology [13]

It utilize co proceed exicipients to develop MDT which dissolves within 30-40 seconds. The technology involves dry blending of drugs, flavor and lubricant followed by compression in to tablets. The tablets obtained have sufficient strenghth so they can be packed in blister packs and bottles. This technology patened by SPI pharma, new castle.

Frosta technology

It utilize the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastics material, water penetration enhancer and binder. The process involves mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The product showed excellent hardness and rapid disintegration within 15-30 seconds. This methodology patented by Akina.

Oraquick

It utilize taste masking microspheres technology called as micro mask, which provides superior mouth feel, significant mechanical strength and quick disintegration and dissolution of the products. This process involves preparation of micro particles in the form of matrix that protects the drug which can be compressed with sufficient mechanical strength. Low heat of

production in this process makes it suitable for heat sensitive drug. The products formed dissolves within few seconds. The methodology patented by K.V Pharmaceuticals.

Ziplets or advatab

It utilize water insoluble gradients combined one are more effective disintegrants to produce MDT s with improved mechanical strength and optimum disintegration time at low compression force. Advantage of the method include high drug loading, formation of coated particles and does not require special packaging. This technology patented by pessano con Bornago.

Flashdose

The flash dose tablets consists of self binding shear form matrix termed as floss. Shear form matrices are prepared by flash heat processing. This technology patented by Fluzisz [8]. Egibuprofen melt in mouth tablets.

1.8.2. Conventional methods

Lyophilization or freeze-drying

Lyophilization is a process which includes removal of a solvent from a frozen suspension of drug with structure forming additives [3]. Freeze drying of a drug along with additives imparts glossy amorphous structure resulting in highly porous and light weight product. The resulting tablet has rapid disintegration and dissolution when placed on a tongue and the freez dried utin dissolves instantly to release the drug. MDT s formed by lyophilization have some demerits like low mechanical strength, poor stability at higher temperature and humidity. Use of expensive equipment for freeze drying is another demerits of the process.

Moulding

Molding process include moistening, dissolving or dispersing the drug with a solvent then molding the moist mixer in to tablets(compression molding with a low pressure than conventional tablet compression evaporating the solvent from drug solution, or suspension at ambient pressure respectively. The molded tablets formed by compression molding are air dried[4]. As the compression force employed is lower than conventional tablet, the molded tablet results in highly porous structure, which increase the disintegration and dissolution of the product. To further improve the dissolution rate of the product powder mixer should be sieved through very fine screen. This process is applied usually with soluble ingredients (saccharides) which offer improved mouth feel and disintegration of tablets. Some of the demerits observed are the tablet formed by this process shows low mechanical strength, which results in erosion and breakage during handling.

Cotton candy process

Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning [3]. The matrix formed is partially recrystallized to have improved flow properties and compressability. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to MDTs. This process is so named because it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. The main merits of this method are the process can accommodate high doses of drug and offers improved mechanical strength. The main demerit is the use of high process temperature.

Spray drying [18]

In this method MDTs formulated by using 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.ie citric acid (an acid) and sodium bicarbonate (an alkali)[4]. The formulation was spray dried to yield a porous powder. The products formed are highly porous fine powders and are disintegrated in<20 seconds [3]. Allen et al utilized this method for preparing MDTs.

Mass extrusion [4]

It 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 in to even segments using heated blade to forms tablets.

Compaction melt granulation

The method involves incorporation of hydrophilic waxy binder (super poly state.) PEG - 6-sterate. Super poly state is a waxy material with an M.P of 33-37 °C and an hydrophilic lipophilic balance of 9. It act as binder, increase the physical resistance of tablets and it helps the disintegration of tablets as it melt in the mouth and solubilizes rapidly leaving no residue. Super poly state incorporated in the formula by melt granulation method, where granules are formed by the molten form of the material. Eg.. crystallized paracetamol was used as model drug and in addition mannitol added as water soluble excipient and cross carmellose sodium as disintegrating agents. Abdlbary et al., prepared MDT by this method.

Phase transition process

Kuno et al investigated disintegration of MDTs are formulated by sugar alcohols using erythriol(M.P 122C),xylitol(m.p 93-95), trehalose(97c) and mannitol (166c). this method involves compressing a powder containing two sugar alcohols with high and low-melting points and subsequent heating at temperature between their melting points. Before heating process the tablet does not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of interparticular bonds or bonding surface area in tablets induced by phase transition of low melting point sugar alcohols.

Sublimation

The method involves addition of volatile salt to the tabletting components, mixing and volatilizing the volatile salt creates pores in the tablets come in contact with saliva. Camphor, naphthalene, urea, ammonium bi carbonate etc.can be used to prepare porous tablets of good mechanical strength. koizumi et al used mannitol as diluents and camphor as volatile material to prepare porous compressed tablet. The tablet were subjected to vaccum at 80 °C for 30 minutes to eliminate camphor and thus forms the pores in the tablet. The tablet formed have highly porous matrix which is the key factor for rapid disintegration.

1.8.3. Other methods

Other methods includes dry granulation, wet granulation and direct compression methods. The important components used in these methods are super disintegrants.

Dry granulation

In this technique there is no use of liquids. The process involves the formation of slugs. Then slugs are screened are milled to produce granules. The granules formed are then compressed to form tablet.

Wet granulation [20]

The process involves addition of liquids to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets. This method have more operational manipulation and is more time consuming than other methods. this method is not suitable for drugs which ass thermo labile or hydrolysable by presence of water in the liquid binder.

Direct compression [18]

In direct compression method, of powder blends of active ingredients and suitable excipients, which will flow uniformly in the die cavity and formed a film compact .direct compression method are very popular because it reduse the number of steps involved and the materials required.

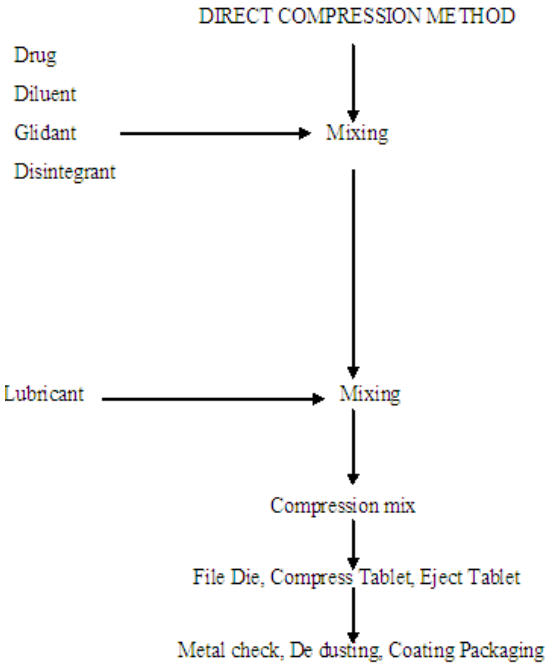

Figure -1: Flow sheet of direct compression

Advantages

- Easiest method to manufacture fast dissolving tablets.
- Low manufacturing cost.
- Use of conventional equipment and commonly available excipients.
- High quality finished product.

1.9. Evaluation of tablets

Weight variation test

The tablet of one particular batch should have uniformity in weight. If any weight variation is found, it should fall within the prescribed limits. According to USP maximum % deviation allowed are as follows:

Table - 1: Limit for Weight Variation Test (USP)

Average weight of tablets(mg)	Maximum % difference allowed
130mg or less	±10%
130-324mg	±7.5%
Above 324mg	±5%

Friability test

20 tablets were weighed and subjected to rotate on friability test apparatus. The drum rotated at a speed of 25 rpm for 4 minutes, then dedusted and reweighed the tablets. Percentage friability was calculated by the following formula [6].

$$\text{Percentage of Friability} = 100(w_0\text{-}w/w_0)$$

Where,

Wo = Initial weight, W = Final weight.

Percentage friability of tablets less than 1% is considered acceptable.

Hardness test

Hardness of a tablet determines its tensile strength. It must be such that the tablets withstand the shock of handling, packing, and shipping. It is measured in terms of load/pressure required to crush it when placed on its edge. Generally, two types of hardness testers are used to determine the hardness. (Eg., Monsanto hardness tester, Pfizer tablet hardness tester).

Thickness test

Control of physical dimension of the tablets such as sizes and thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. Manufacturers set the limits on the thickness of the tablets of their products in order to avoid any problems during automatic counting and packing. If the thickness of the tablet goes beyond a certain limit, it may block the channels of the machines. Hence there should be in-process control to maintain the thickness of the tablets. The dimensional specifications were measured using vernier calipers.

Disintegration time

The test is performed *invitro* to determine the time in which a tablet disintegrates in the simulated GIF fluid at the 37±2°C. The apparatus which is used to simulated all the conditions of alimentary canal, for the determination of disintegration time is called as Disintegration Time Apparatus.

Dissolution

Dissolution is defined as a process in which a solid substance solubilizes in a given solvent; mass transfer from solid surface to the liquid phase. The development of dissolution methods for ODTs is comparable with the approach taken for conventional tablets and is practically identical [4].

2. CONCLUSION

The goal of mouth dissolving tablets is to achieve faster action compare to conventional dosage form is a major advantage of this system. The Mouth dissolving consists super disintegrants which we can balance the faster disintegration and suitable hardness of the tablets. This is the promising approach for all the class of drugs which necessary to produce faster action. The mouth dissolving tablets can be dissolved in mouth within a few seconds and it can able to produce faster onset of action. It can be formulated by using commercially available disintegrants and excipients by direct compression techniques. The mouth dissolving tablets can be easily developed and commercialized.

Table - 2: marketed products of mouth dissolving tablets

Product	Active drug	manufacture	use
Felden FM	Piroxicum	Pfizer,NY,U.S.A	Relieves pain & inflamation
Torrox MT	Rofecoxib	Torrentpharma, ahmedadad, india.	Non-steroidal anti-inflammaatory drug.
Nimulid MD	Nimesulide	Panacea, newdelhi, india.	Analgesic& antipyretic.
Valus	Valdecoxib	Galen mark	Analgesic& antipyretic.
Olanex instab	Olanzapine	Ranbaxy labs ltd, newdelhi, india.	Anti psychotic drug
Rofixx MD	Rofecoxib	Cibla ltd.,	anti-inflammaatory drug.
Romilast	Motelukast	Ranbaxy labs ltd, newdelhi, india	Rinasthma& allergy.
Pepcid RPD	Famotidine	Merck pharma,NJ,U.S.A	Heatburns& duodenal ulcer.
Lonazep MD	Olnazapine	Sunpharma	Anti epileptic drug
Febrectol	Paracetamol	Prographarm, chateauneuf, france.	Analgesic& antipyretic.

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