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Review Article

A REVIEW ON FORMULATION PARAMETER OF FAST DISSOLVING TABLET

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Abstract:

Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. The choice of excipients in tablet formulations depends on the API, the type of tablet, the desired characteristics, and the manufacturing process used. This is especially important for immediate release products where rapid release of drug substance is required. A disintegrant can be added to a powder blend for direct compression or encapsulation. A Fast Mouth Dissolving Tablet (FMDT) can be defined as an oral solid dosage form which when placed on tongue, disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and then swallowed. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down in to the stomach. A process in which water is sublimated from the product after freezing is called freeze drying. Freeze dried forms offer more rapid dissolution than other available solid products. Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent it dissolves in the molten carrier. Spray drying technique is based upon a particulate support matrix and other components to form a highly porous and fine powder. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water-soluble excipients and effervescent agent, disintegrant efficacy is strongly affected by tablet size and hardness.

Keywords: Fast mouth dissolving tablet; Superdisintegrants; Orodispersible; Mouth dissolving tablets

INTRODUCTION

The drugs that are administered orally, solid oral dosage form represent the preferred class of products. The reasons for this preference are as follows. Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patient[1].

CHOICE OF EXCIPIENTS:

The choice of excipients in tablet formulations depends on the API, the type of tablet, the desired characteristics, and the manufacturing process used. Several types of tablets are available in the market. These include prompt release, from which the drug dissolves in a very short time (sublingual or buccal tablets), and immediate release and modified release, which includes most of the oral administered tablets that are swallowed. Other types include effervescent, belayed, chewable, multiple compressed topical tablets and tablets for solution. The desired characteristics of a tablet may be achieved by adding colors, pigments, flavours, sweetners and a sugar or film coating. The types of excipients -selected for a formulation depend on the basic process used to manufacture the tablets.

DRUG-EXCIPIENT INTERACTIONS AND THEIR EFFECT ON ABSORPTION:

Excipients are traditionally thought of as inert but they can have tremendous impact on the ultimate pharmacological availability of a drug substance when added to a formulation. The magnitude of this effect will depend on the characteristics of the drug and on the quantity and properties of the excipients. Excipients have traditionally been classified according to the formulation they perform in a formulation, although many excipients perform multiple functions. Diluents allow the formulation of a practically sized tablet and can form large proportion by weight of a formulated product when, for example, the active ingredient is very potent. The physical characteristics of the diluents are important; for example, triamterene was shown to dissolve more rapidly when it was formulated with hydrophilic fillers such as lactose and starch as compared with insoluble diluents. Disintegrants tend to swell when wetted and so are added to a formulation to facilitate the breakdown of the dosage form into granules and powder particles. The newer disintegrants, called superdisintegrants, cause an extremely rapid break up of a tablet owing to their ability to swell to many times their original size. Wicking and swelling were

found to be the primary mechanisms of actions for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas etc., may play a role in particular cases of tablet disintegration (kanig and Rudnic,1984). Co processing is defined as combining or more established excipients by an appropriate. Coprocessing of excipient could lead to formation of excipients with superior properties compared with the simple physical mixtures of their components or with individual components. A large number of coprocessed diluents are commercially available. The representative examples are Ludipress, Cellactose and starlac. The use of coprocessing is totally unexplored avenues in disintegrants. The widely used super disintegrants are SSG, crosspovidone and crosscarmellose sodium. Like diluents each super disintegrants have strengths and weakness.

SUPER DISINTEGRANTS IN IMMEDIATE RELEASE TABLETS:

A disintegrant is an excipient which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment. This is especially important for immediate release products where rapid release of drug substance is required. A disintegrant can be added to a powder blend for direct compression or encapsulation. It can also be used with products that are wet granulated. While there are some tablets fillers (starch, MCC) which aid in disintegration, there are more effective agents referred to as superdisintegrants.

METHOD OF ADDITION OF DISINTEGRANTS:

The requirement placed on the tablet disintegration should be clearly defined. The ideal disintegrant has,

1. Poor solubility.
2. Poor gel formation.
3. Good hydration capacity.
4. Good molding and flow properties.
5. No tendency to form complexes.

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment. There are two methods of incorporating disintegrating agents into tablets:

- Internal addition
- External addition
- Partly internal and external

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In internal addition method, the disintegrant is mixed with other powders before wetting the powder mixture with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used part of the disintegrants are added internally and part externally. This provides immediate dispersion of the tablet into previous compressed granules while the disintegrating agents within the granules produce further erosion of the granules to the original powder particles. The two stepped method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

FAST MOUTH DISSOLVING TABLET:

Most commonly employed oral dosage forms are tablets and capsules. Compressed tablets are the most widely used dosage forms for a number of reasons. They are convenient, easy to use, less expensive, tamper-proof, easy to pack and ship and more stable than other oral dosage forms. Also tablets lend themselves to certain special release profile products such as enteric or delayed release products.[1]

A Fast Mouth Dissolving Tablet (FMDT) can be defined as an oral solid dosage form which when placed on tongue, disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and then swallowed. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down in to the stomach. The main problem with the common oral dosage forms is that they have to be swallowed along with water. Many patients find it difficult to swallow tablets, especially in elderly and pediatrics, because of the physiological changes associated with these groups. Due to this dysphagic condition, they do not comply with prescription which results in patient non-compliance. The other causes of patient non-compliance include sudden episodes of allergic attacks, motion sickness, coughing and unavailability of water etc. These problems can be resolved by fast dissolving tablets, which do not require water to aid in swallowing.

'Fast Dissolve', 'Quick Dissolve', 'Rapid Melt', 'Quick Disintegrating', 'Mouth Dissolving', 'Orally Disintegrating', 'Oro Dispersible', 'Melt-in Mouth' etc. Are terms that represent the same drug delivery systems? Recently Orally Disintegrating (OD) Tablet technology has been approved by United States Pharmacopoeia (USP), Centre for Drug Evaluation and Research (CDER). USFDA defined OD tablet as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia also adopted the term "Oro Dispersible tablet" as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing. These dosage forms dissolve or disintegrate in the patient's mouth within 15 seconds to 3 minutes without the need of water or chewing. Despite various terminologies used, Oro Dispersible tablets are here to offer unique form of drug delivery with many advantages over the conventional oral solid dosage forms.

Advantages of Fast Mouth Dissolving Tablets:

a) **Ease of swallowing**: Dysphagic population constitute 35% of the general population, since this disorder is associated with a number of medical conditions such as Stroke, Parkinson's disease, AIDS, Head and Neck Radiation Therapy and other neurological disorders.

b) **No water needed:** These fast dissolve dosage forms 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.

c) **Superior taste**: Most fast dissolve dosage forms contains taste-masked active ingredient, usually sweetening agent and a flavor.

d) **Accurate dose**: The fast dissolve dosage forms have the added advantages of convenience and accurate dosing as compared to liquids.

e) More rapid drug absorption through pre-gastric absorption from the mouth, pharynx and esophagus.

f) Rapid drug therapy intervention is possible.

g) New business opportunities like product differentiation, line extension and life cycle management, exclusivity of product promotion.

Characteristics of ideal Fast Dissolving Tablets:

- They should not require water for administration, yet dissolve or disintegrate in the mouth within a few seconds.
- They should be compatible with taste masking.
- They should be portable without fragility concerns.
- They should have a pleasing mouth feel.
- They should leave minimal or no residue in the mouth after oral administration.
- They should allow high drug loading
- They should exhibit low sensitivity to environmental conditions such as humidity and temperature.
- They should be manufactured using conventional tablet processing and packaging equipments at low cost.

To ensure the tablet's fast dissolving attribute, water must quickly egress into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. Maximizing the porous structure of the tablet matrix and incorporating an appropriate disintegrating agents or highly water soluble excipients in the tablet formulation are the basic approaches used in current fast dissolving tablet technologies. Basically, the disintegrants major function is to oppose the efficacy of the tablet binder and the physical forces that act under compression to form the tablet. The mechanism by which tablet is broken down into smaller particles and then produces a homogeneous suspension or solution is based on:

I) Capillary action
II) High swellability of disintegrants
III) Capillary action and high swellability
IV) Chemical reaction (Release of Gases)

Conventional technologies for preparing mouth dissolving tablets:

Freeze Drying:

A process in which water is sublimated from the product after freezing is called freeze drying. Freeze dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation. However, the use of freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs. A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapse temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying of the tablet above its collapse temperature instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva.

Moulding:

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent it dissolves in the molten carrier. The drug can exist as discrete particles or micro particles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is, generally made from water-soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

Sublimation:

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed. Inert solid ingredients (E.g. urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use.

Spray Drying:

Highly porous and fine powders can be produced by spray drying, as the processing solvent is evaporated rapidly during spray drying. Spray drying technique is based upon a particulate support matrix and other components to form a highly porous and fine powder. This is then mixed with above ingredients and compressed to tablet. The fast dissolving tablets prepared form Spray drying technique disintegrated within 20 seconds.

Mass Extrusion:

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.

Direct compression:

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water-soluble excipients and effervescent agent, disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and/or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance

Table 1: Various commercially available super disintegrants along with their properties patented technologies for orodispersible or mouth dissolving tablets

S. no	Name	Type	Properties	Brand name
1	Crospovidone	Polyvinyl-pyrrolidone	Crossed linked Polyvinyl pyrrolidone Rapidly disperses and swells in water	Polyplasdone XL, Kollidon CL
2	Croscarmellose Sodium.	Modified cellulose	Cross linked sodium carboxy methyl cellulose.Excellent swelling and water wicking properties	Ac-di-sol, Primellose, Solutab.
3	Sodium starch Glycolate	Modified starch	Sodium salt of carboxy methyl ether of starch. High swelling capacity and rapid water uptake	Primogel, Explotab glycilys

ZYDIS Technology:

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

DURASOLV Technology:

Durasolv 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 using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring small amounts of active ingredients.

ORASOLV Technology:

CIMA labs have developed Orasolv Technology. 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 prepare the tablets. The tablets prepared are soft and friable and packed in specially designed pick and place system.

FLASH DOSE Technology:

This technology is based on the preparation of sugar based matrix known as floss, which is made from a combination of excipients either alone or in combination of drugs. Two platform fuisz technologies called Sheaform or Ceform are currently being utilized in preparation of wide range of oral disintegrating product.

Flash dose has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets; prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consists of self-binding shearform matrix termed as "Floss". Shear form matrices are prepared by flash heat processing.

WOWTAB Technology:

Wow tab Technology is patented by Yamanouchi Pharmaceutical Company 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 and granulated with a high mouldability saccharide and compressed into tablet.

FLASHTAB Technology:

Prographarm laboratories have patented the Flash tab technology. Tablets prepared by this method will contain active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion-spheronisation etc.

CEFORM Technology:

In this, microspheres containing active ingredient are prepared. The manufacturing process involves placing a dry powder, containing either substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into precision engineered, and rapidly spinning machine. The centrifugal force throws dry blend at high speed through small, heated openings. The resultant microburst of heat liquifies the drug blend to form sphere. The microspheres are blended or compressed into preselected oral delivery dosage form. The microspheres can be incorporated into a wide range of fast dissolving dosage forms such as flash dose, or spoon dose, EZ chew.

SHEARFORM Technology:

Shear form technology is based on preparation of floss that is also known as "Shear form Matrix", which is produced by subjecting a feedstock containing a sugar carrier to flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal flow condition, which permits part of it to move with respect of the mass. The flowing mass exits through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further cropped and recrystallised by various techniques to provide uniform flow properties and then facilitates blending. The recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallisation. The Shear form floss, when blended with the coated or uncoated microspheres, is compressed into tablets or EZ chewable tablets from standard tableting equipment.

Cotton candy:

Cotton candy process is known as candy floss process .this technique forms the basis of flash dose (Fuss technologies, Chantilly, VA) in this technology, saccharides or polysaccharides are processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The floss is then partially recrystallised to impart a good flow properties and compressibility the floss then can be milled and blended with active ingredient and other excipients and finally that compressed into MDT. Advantages of this process are that the tablet can be accommodate high doses and posses satisfactory mechanical strength .The candy floss are hygroscopic, hence, their manufacturing requires control of humidity conditions.

Table 2: Comparison of some patented technologies for mouth dissolving tablets[15]

Technology	Novelty	Handling /storage	Drug release /bio availability
Zydis(R.P Scherer, Inc.)	First to market. Freeze Dried	Do not push tablet through foil. Do not use dosage form from Damaged package. Sensitive to degradation at humidities >65%	Dissolves in 2 to 10 seconds. May allow for pre gastric absorption leading to enhanced bio availability
Orasolv (CIMA labs,inc)	Unique taste Masking packs Lightly compressed	Packaged in patented foil packs	Disintegrates in 5 to 45seconds depending upon the size of the tablet.No significant Change drug bioavailability
Durasolv (CIMA Labs, Inc.)	Similar to Orasolv, but with better mechanical strength	Packaged in foil or bottles packaged in bottles, avoid exposure to moisture or humidity	Disintegrates in 5 to 45 seconds depending upon the size of the tablet. No significant change in drug bioavailability
Wowtab (YAMANOUCHI Pharma Technologies, Inc.)	Compressed dosage form. Proprietary taste masking. Smooth melt action gives superior mouth feel.	Package in bottles. Avoid exposure to moisture or humidity	Disintegrates in 5 to 45seconds up on the size of the tablet. depending No significant change in drug bio availability in drug bioavailability

Table 3: List of commercially available orodispersible tablets

Trade Name	Active Drug	Manufacturer
Feldene Fast Melt	Piroxicam	Pfizer Inc., USA
Calritin Redi Tab	Loratidine	Schering Plugh Corp, USA
Maxalt MLT	Rizatriptan	Merck & Co. USA
Zyprexia	Olanzapine	Eli Lilly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck & Co., NJ, USA
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Tempra Quiclets	Acetaminophen	Bristol Myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New Delhi, India
Romilast	Montelukast	Ranbaxy Labs Ltd., New Delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephendrin	Warner Lambert, USA

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