
MOUTH DISSOLVING TABLETS, SOLID DISPERSIONS: METHODS TO INCREASE ORAL BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach market due to their poor water solubility. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The desire of the improved palatability in orally administered products has prompted the development of numerous formulations with improved performance and acceptability. Mouth dissolving tablets (MDTs) and Solid dispersion technique have received ever increasing demand during the last few decades, and the field has become a rapidly growing area in the pharmaceutical industry. The oral bioavailability of BCS (biopharmaceutics classification system) class II drugs with poor solubility and reasonable permeability is limited by the drug dissolution step from drug products. A variety of dosage forms like tablets, films, wafers, chewing gums, microparticles, nanoparticles etc. have been developed for enhancing the performance attributes in the orally disintegrating systems. This review depicts the various aspects of MDT formulation and various preparation techniques for solid dispersion.

Key Words: Mouth Dissolving Tablets; Superdisintegrants; Patented Technology; Solid Dispersion.

INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness of self administration, compactness and easy manufacturing.[1] MDTs with good flavor increases the acceptability of bitter drugs by various groups of population. MDT has been investigated for their potential in improving bioavailability of poorly soluble drug through enhancing the dissolution profile of the drug and hepatic metabolism drugs. United States food and drug administration (FDA) defined MDT 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." The disintegration time for MDTs generally ranges from several seconds to about a minute.[2] In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor.[3] The solubility of a drug is a key determined of its oral bioavailability and permeability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin , digoxin, phenytoin, sulphathiazole come immediately to mind. To enhance bioavailability of poorly soluble drugs. Solid dispersion as a formulation approach. A term solid dispersion refers to a group of solid

products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. Bioavailability is one of the important parameter to achieve desired concentration of drug in systematic circulation for pharmacological response to be shown. A drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor solubility of dissolved drug at physiological pH, poor permeation through biomembrane, extensive presystemic metabolism. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first pass metabolism, pre systemic metabolism and susceptibility to efflux mechanisms. [4] Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.

BCS classification [5]

Class I: high permeability and solubility.

Class II: high permeability but low solubility.

Class III: low permeability but high solubility.

Class IV: low permeability and low solubility.

To enhance the oral bioavailability following are the two given below descriptions:

1. **Mouth dissolving tablets**
2. **Solid dispersion technique**

A) Mouth dissolving tablet

Requirements for the MDTs as are:[6]

1. Require no water for oral administration, yet dissolve /disperse /disintegrate in mouth in a matter of seconds.
2. Have a pleasing mouth feel.
3. Have an acceptable taste masking property.
4. be harder and less friable.
5. Leave minimal or no residue in mouth after administration.
6. Exhibit low sensitivity to environmental condition (temperature and humidity).
7. Allow the manufacture of tablet using conventional processing and packaging equipments.

Advantages of mouth dissolving tablet:

1. No need of water to swallow the tablet.[7]
2. Can be easily administered to pediatric, elderly and mentally disabled patients.
3. Accurate dosing as compared to liquids.
4. Dissolution and absorption of drug is fast, offering rapid onset of action. [8]
5. Bioavailability of drugs is increased as some drugs are absorbed from mouth. Pharynx and esophagus through saliva passing down into the stomach.[9]

6. Advantageous over liquid medication in terms of administration as well as transportation
7. First pass metabolism is reduced , thus offering improved bioavailability and thus reduced dose and side effects.

Ideal properties of MDTs

1. MDT should not require water or other liquid to swallow. [10]
2. It should easily dissolve or disintegrate in saliva within a few seconds.
3. Have a pleasing taste.
4. Leave negligible or no residue in the mouth when administered.
5. Be portable and easy to transport.
6. Be able to be manufactured in a simple conventional manner within low cost.
7. Be less sensitive to environmental conditions like temperature, humidity .[11]

VARIOUS TECHNIQUES FOR “MDT” PREPARATION:

Many techniques are used for the preparation of fast dissolving tablets which are shown in below given table:[12,13]

Table 1 : Different techniques with method and characteristics of prepared fast dissolving table.

| Techniques | Method and characteristics of prepared MDT |
|--|---|
| Disintegrant addition | Involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. For eg MCC and sodium starch glycolate are used in formulation of efavirenz, crystalline cellulose and low substituted HPEC used in oxybutinin and pirenzepine formulation. Crosspovidone used in galanthamine HBr. Crosspovidone (3%w/w) and crosscarmallose Na (5%w/w) used in prochlorperazine maleate formulation. Characteristics: similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability. |
| 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 Characteristics: the preparation is highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability. |
| Moulding | Water soluble ingredients with a hydro alcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression. Characteristics: molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased. |
| Sublimation | Inert solid ingredients that volatilize rapidly like urea ,Camphor ammonium carbonate, ammonium bicarbonate, were added to the other tablet ingredients and the mixture is compressed into tablets . the volatile materials were then removed via sublimation, which generates porous structure. Characteristics: porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc. |
| Spray drying | By hydrolysed and gelatins as supporting agents mannitol as bulking agent, sodium starch glycolate or crosscarmallose sodium as disintegrating agent and an acidic material (eg citric acid)and/ or alkali material (e.g sodium bicarbonate) to enhance disintegration / dissolution. Characteristics : prepared tablet disintegrates within 20 sec, when immersed in an aqueous medium. |
| Mass –extrusion | Involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blades to form tablets. Characteristics: the dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste |
| Direct compression | Conventional equipment , commonly available excipients and a limited number of processing steps are involved in direct compression. Characteristics: it is most cost effective tablet manufacturing technique. |
| Cotton candy process | Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to MDT. Characteristics : it can accommodate high doses of drug and offers improved mechanical strength. |
| Compaction; Melt granulation | Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-G-sterate, super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration tablet. Characteristics : it melts in the mouth and solubilizes rapidly leaving no residue. Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter |

| | |
|----------------------------------|---|
| Phase –transition process | particle bond induced by phase transition of lower melting point sugar alcohol. Characteristics : the compatibility increased and so sufficient hardness gained by the formulation. |
| Nanonization | Involve size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surfaces adsorption on stabilizers, which are then incorporated into MDTs. Characteristics : it is used for poorly water soluble drugs . it leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wider range of doses (up to 200 mg of drug per unit). |
| Fast dissolving films | A non aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethyl cellulose , hydroxypropyl methyl cellulose , hydroxy 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 film. Characteristics : the thin film size less than 2×2 inches , dissolution in 5 sec, instant drug delivery and flavored after taste. |

TABLE 2. SOME PATENTED TECHNOLOGIE

| FORMULATION | KEY ATTRIBUTES | COMPANY |
|------------------------------|---|---|
| Zydis[®] | Freeze-drying on blister packing | RP Scherer (cardinal) |
| Lyoc | Freeze-drying on the shelves of freeze dryer | Laboratories L. Lafon, Maisons Alfort, France |
| Flashtab | Granulation of excipients by wet or dry granulation method and followed by compressing into tablets | Ethypharm France. |
| OraSolv | Low compression force and an effervescent couple as a water –soluble disintegrating agent | Cima Labs Inc. |
| DuraSolv | Direct compression using water –soluble excipients | Cima Labs Inc |
| WOWTAB[®] | High- and Low – moldability saccharides | Yamanouchi Pharma |
| Pharmabrust | Direct compression of powder mixture | SPI Pharma |
| AdvantolTM | Directly compressible excipient system | SPI Pharma |
| Advatab[®] | Directly compression using external lubrication system | Eurand |

TABLE.3 LIST OF SOME COMERICALLY AVAILABLE FAST DISSOLVING TABLETS

| Trade name | Active drug | manufacturer |
|--------------------------|--------------|--------------------------------|
| Felden fast melt | Piroxicam | Pfizer Inc., NY , USA |
| Claritin redi Tab | Loratidine | Schering plough Corp., USA |
| Maxalt, MLT | Rizatriptan | Merck and Co., NJ ,USA |
| Zyprexa | Olanzapine | Eli lilly. Indianapolis , USA |
| Pepcid RPD | Famotidine | Merck and Co ., NJ , USA |
| Zofran ODT | Ondansetron | Glaxo Wellcome, Middle sex, UK |
| Zomin ZMT | Zolmitriptan | Astrazeneca, Wilmington, USA |

TABLE 4: LIST OF SUPERDISINTEGRANTS

| Super disintegrants | Example | Mechanism of action | Special comment |
|---|---------------------------|--|--|
| croscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab® Vivasol®L-hpc | Cross linked cellulose | Swells 4-8 folds in <10 seconds -swelling and wicking both | -swells in two dimensions. -direct compression or granulation -starch free |
| Crosspovidone Crosspovidone M® kollidon® Polyplasdone® | Cross linked PVP | -Swells very little and returns to original size after compression but act by capillary action | -water insoluble and spongy in nature so get porous tablet |
| Sodium starch glycolate Explotab® Primogel® | Cross linked starch | -swells 7-12 folds in<30 seconds | -swells in three dimensions and high level serve as sustain release matrix |
| Aliginic acid NF Satialgine® | Cross linked alginic acid | -rapid swelling in aqueous medium or wicking action | -promote disintegration in either dry or wet granulation |

LIMITATIONS OF MOUTH DISSOLVING TABLETS

The tablets usually have insufficient mechanical strength hence, careful handling is required.

The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

SOLID DISPERSION:

Definition: In 1971 Chiou and Riegelman defined solid dispersion as “the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method”. The solid dispersions may also be called solid-state dispersions, as first used by Meyersohn and Gibaldi (1966)[15]

ADVANTAGES AND DISADVANTAGES OF SOLID DISPERSION.[14]

Advantages – increase in dissolution rate & extent of absorption and reduction in pre systemic metabolism. Transformation of liquid form of drug into solid form. Ex. Clofibrate & benzyl benzoate incorporated into PEG-6000 to give solid dispersion also avoidance of polymorphic changes so no bioavailability problems (as in case of nabilone & PVP dispersions).

Disadvantages: major problem is instability. There is change in crystallinity & decrease in dissolution rate with aging. Ex. Crystallization of ritonavir from supersaturated solution in solid dispersion system (main reason for withdrawal of ritonavir capsules [Norvir, Abbott] from market.)

TABLE 5: TYPES OF SOLID DESPERSION. [16]

| | Solid dispersion type | Matrix * | Drug ** | Remarks | No. phases |
|----------|--|-----------------|----------------|--|-------------------|
| 1 | Eutectics | C | C | The first type of solid dispersion prepared. | 2 |
| 2 | Amorphous precipitations in crystalline matrix | C | A | Rarely | 2 |
| 3 | Solid solutions | | | | |
| | Continuous solid solutions | C | M | Miscible at all composition, never prepared | 1 |
| | Discontinuous solid solutions | C | M | Partially miscible, 2 phases even though drug is molecularly dispersed. | 2 |
| | Substitutional solid solutions | C | M | Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed. | 1 or 2 |
| | Interstitial solid solutions | C | M | Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example :drug in helical interstitial spaces of PEG. | 2 |
| 4 | Glass suspension | A | C | Particle size of dispersed phase dependent on cooling /evaporation rate. Obtained after crystallization of drug in amorphous matrix. | 2 |
| 5 | Glass suspension | A | A | Particle size of dispersed phase dependent on cooling /evaporation rate many solid dispersions are of this type | 2 |
| 6 | Glass solution | A | A | Requires miscibility OR solid solubility, complex formation or upon Fast cooling OR evaporation during preparation , many (recent) examples especially with PVP. | 1 |

*A: matrix in the amorphous state , C: matrix in the crystalline state

**A: drug dispersed as amorphous clusters in the matrix, C : drug dispersed as crystalline particles in the matrix , M: drug molecularly dispersed throughout the matrix.

METHODS OF SOLID DISPERSION PREPARATION [17-20]

Melting and solvent evaporation methods are the two major processes of preparing solid dispersion.

Melting method: Sekiguchi et al were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drugs incorporation [31]

Hot stage extrusion: Hot stage extrusion has in recent years gained wide acceptance as a method of choice for the preparation of solid dispersions. The hot stage extrusion process is highly dependent on the physicochemical properties of the compounds and their miscibility in the molten state. Hot-stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. Extrusion then collected after cooling at room temperature and milled.[21,20,22] Moreover, it was observed that solid dispersions of itec SPI prepared by hot- stage extrusion presented itraconazole in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by drying[20].

Melt agglomeration: Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excipients [23]. It is prepared by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier [24]. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor [17].

Solvent evaporation method: The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated [25-27]. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature [19]. A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol, chloroform, mixture of ethanol and dichloro methane. Normally, the resulting films are pulverized and milled [26,27].

Spray drying: Spray drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving [20, 28, 29] or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent [20, 28]. Due to the large

specific area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation..

Freeze drying: This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen, then, the frozen solution is further lyophilized. [30,31]. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices [32], the technique is poorly soluble exploited for the preparation of solid dispersions. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. The risk of phase separation is minimized.

Supercritical fluid method: Supercritical fluid methods are mostly applied with carbon dioxide (CO₂), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO₂. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel [19].

Co-precipitation method: Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method non-solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non solvent addition, the drug and carrier are co-precipitated to form microparticles. At the end, the resulted micro particle suspension is filtered and dried [33]. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The solution was dried under vacuum at room temperature and kept inside incubator (37°C) for 12 hrs. Finally it was passed through sieves.

Dropping method: This technique may overcome some of the difficulties inherent in the other method. This method was developed [34]. To facilitate the crystallization of different chemicals is a new procedure for producing round particles from melted solid dispersions. A solid dispersion of a melted drug carrier mixture is pipette and then dropped in to a plate, where it solidifies into round particles. This method also avoids the pulverization, sifting and compressibility dispersion.

CONCLUSION: The bioavailability of the drug is the most important factor that controls that control the formulation of the drug as well as

therapeutic efficacy of the drug, hence the most critical factor in the formulation development. As per the formulation point of view mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. The delivery of poorly water-soluble drug has been the subject of much research, as approximately 40% of new chemical entities are hydrophobic in nature and solubility of active pharmaceutical ingredients has always been a concern for formulators. Because of the solubility problem of many drugs the bioavailability gets affected and hence solubility enhancement becomes necessary. It is now possible to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above. Numerous technological advancements have

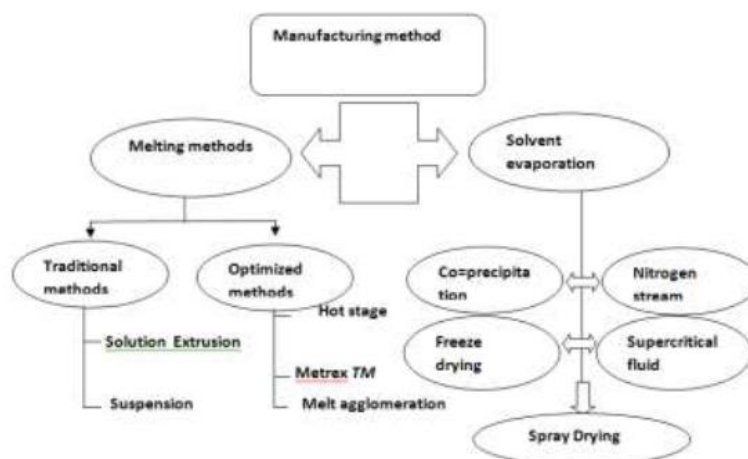
been introduced for solubility and dissolution enhancement of poorly soluble drugs.

CHARACTERIZATION OF SOLID DISPERSION [35]

The most important methods which are used for characterization are thermo analytical, x-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. Method for the characterization of solid dispersions is as following

1. Dissolution testing.
2. Thermo analytical methods: differential thermo analysis and hot stage microscopy.
3. Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change.
4. X-ray diffraction.
5. Spectroscopic methods, e.g. IR spectroscopy, NMR spectroscopy.
6. Microscopic methods including polarization microscopy and scanning electron microscopy

Figure: METHODS OF PREPARATION OF SOLID DISPERSION



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