Review Article
Formulation of Mouth Dissolving Tablets Using Solid Dispersion Technique: A Review

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ABSTRACT
Mouth-dissolving tablets are also called as fast disintegrating tablets, melt-in mouth tablets, orodispersible tablets, quick dissolving etc. Mouth dissolving tablets are those when put on tongue disintegrate rapidly thereby releasing the drug, which dissolve or disperses in the saliva. The faster the drug dissolved into solution, quick will be the absorption and onset of clinical effect. Mouth dissolving tablet containing solid dispersion was developed to improve the solubility of drug and stability of solid dispersion. Such tablets are disintegrate and/or dissolve rapidly in the saliva without the need for water. Hence it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. The later portion of the article focus on the progress in methods of manufacturing, evaluation and various latest technologies involved in the development of Mouth dissolving tablets. Solid dispersion is basically a drug with polymer two-component system; hence the drug–polymer interaction should be determined first in order to ensure the stability of the formulation. This review is intended to discuss the recent advances related on the area of solid dispersion technology. Since different methods are used for the preparation of solid dispersions such as fusion method, solvent method, melting solvent method, melt extrusion method, lyophilisation technique, melt agglomeration process, use of surfactant, electro spinning and super Critical Fluid Technology, of them which method is good and suitable for which type of drug. The use of Mouth dissolving dosage forms has solved various problems noted in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world’s population. The initial focus of this review article is based on solid dispersion mainly advantages, disadvantages, types, the method of preparation, and characterization of the solid dispersion at laboratory and industrial level.

Introduction

Oral routes of drug administration are widely used up to 50-60% of total dosage forms. Solid dosage forms are more popular because of ease of administration, accurate dosage, self-medication, pain avoidance and the patient compliance. Since the most popular solid dosage forms are being tablets and capsules but one important drawback of such dosage forms for some patients, is the difficulty to swallow [1]. Drinking water plays an important role in the swallowing of such oral dosage forms. Oftenly patients feels inconvenience in swallowing conventional dosage forms such as tablet, capsule when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis [2]. For such reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. MDT is not only impressive for people who have swallowing difficulties, but also are ideal for active people [3]. Mouth dissolving tablets are also called as fast-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva [4].

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The faster the drug into solution, quicker the absorption and onset of action. Various drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the GIT [5]. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form due to low hepatic first pass metabolism. Several orally administered drugs have a reduced bioavailability due to their poor water solubility. In biopharmaceutical classification system drugs with low aqueous solubility, slow dissolution rate, high dose, and high membrane permeability are categorized as Class II drug [6]. To overcome low bioavailability, many of the modern oral drug delivery systems work on formulation strategies such as alteration of solvent composition, carrier systems as well as chemical and physical modifications[7].

Solubility enhancement occupies an important place especially in regard to poorly soluble drugs and in absence of proper water solubility the bioavailability of some useful and important drugs remains a problem.

**Solubility Enhancement** [8-11]

Solubility enhancement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.

**Physical Modifications:** These include reduction in particle size like micronization and Nanonisation, modification of the crystal habit like polymorphs, amorphous form etc., drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

**Particle Size Reduction**

The solubility of drug is often related to particle size of drug; as a particle becomes smaller, the surface area to volume ratio increases. The large surface area permits greater interaction with the solvent which causes an increase in solubility. A conventional method of particle size reduction, such as comminution and spray drying, depends upon mechanical stress to disaggregate the active compound. Particle size reduction is thus allowing an efficient, reproducible, and economic means of solubility enhancement.

**Micronization**

The particle size reduction enhance the solubility and dissolution rate of poorly water soluble drugs due to the enhancement in surface area. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill).

**Nanonisation**

It is a process whereby the drug powder is converted to nanocrystals of sizes 200-600 nm. The nanocrystals yield as a dispersion of drug nanocrystals in a liquid, typically called “nanosuspension” [12].

**Modification of the crystal habit**

The surface area of drug available for dissolution depends on its particle size and its ability to be wetted by luminal fluids. This particle size is critically depends on the conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. The comminution techniques can produce particles which are highly heterogeneous, charged, and cohesive, with the potential to cause problems in downstream processing and product performance. Hence, these crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy [13]. By altering the crystallization conditions (by using different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs.

**Amorphous forms**

They have atoms or molecules randomly placed as in a liquid and have higher thermodynamic energy than corresponding crystalline forms. Solubilities as well as dissolution rates are generally higher than crystalline forms.

**Drug Dispersion**

By formulating solid solution, solid dispersion & eutectic mixture one can increase the solubility thereby bioavailability of drug from dosage form.

**Solid dispersions**

In this technique, a poorly water soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield either eutectic (non molecular level mixing) or solid solution (molecular level mixing) products. Solid dispersions are prepared by using several methods including the fusion (melt) method and the solvent method. We know solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is commercially available.

**Solid solution**

A solid solution consist of a poorly aqueous-soluble drug or a solid solvent having solid solute dissolved in it which have good water solubility are comparable to the liquid solution which improve dissolution of a drug to a greater extent. Solid solutions are resultant single phase, which come into being when two compounds disperse in each other at their molecular level [14]. Solid solutions formed by combination of water insoluble carriers with highly water soluble carrier makes surety of having better dissolution rate comparable to the eutectic mixtures, the reason behind that the drug particle size is condensed to molecular level.

**Simple eutectic mixtures**

Eutectic mixture involves mixing of two compounds, which are completely miscible in their liquid state but negligibly in the solid state. They are formed by melting such compounds followed by rapid cooling of the mixture to obtain a physical mixture with fine crystals of both compounds. When the eutectic mixture is subjected to aqueous medium, the water soluble carrier dissolves and releases drug in fine crystalline form & thus improving its aqueous solubility.

**Cryogenic Techniques**

**Supercritical fluid recrystallisation**

The application of supercritical fluid processes, a novel nanosizing and solubilization technology has increased in recent years via particle size reduction. Supercritical fluids (e.g.: carbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), which allow it to assume the properties of both a liquid and a gas.
Spray freezing into liquid (SFL)
This technique involves atomization of an aqueous, organic, aqueous-organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO₂, helium, propane, ethane), or in the cryogenic liquids (i.e. nitrogen, argon or hydrofluoroethers).

Chemical Modifications: It includes change of ph, use of buffer, derivatization, complexation, and salt formation.

Change of pH
pH of solvent when reduced cause increases in solubility. Buffered aspirin tablets are more soluble than plain aspirin tablets.

Use of hydrates or solvates
Usually crystalline compound contain either a stoichiometric or non-stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. Stoichiometric adduct which commonly called “Solvate”, is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water then the complex is called as “hydrate”. A compound not having any water within its crystal structure is termed “anhydrous”. Aqueous solubilities of anhydrous forms are generally higher than the hydrate forms.

Chemical modification of the drug
It is done by the addition of polar groups like carboxylic acids, ketones and amines which increase solubility by increasing hydrogen bonding and the interaction with water.

Change in dielectric constant of solvent
The addition of a cosolvent can increase solubility of water hating molecules by reducing the dielectric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant hence widely used.

Inclusion complexes or clathrates
Significant increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. β-Cyclodextrins can solubilize water insoluble drugs.

Miscellaneous Methods: These include supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotropy, and novel excipients.

Co-solvency
Weak electrolytes and non polar molecules usually have poor water solubility. Their solubility can be increased by the addition of water miscible solvent in which the drug has good solubility. This process of improving solubility is known as cosolvency and the solvents used in combination to increase the solubility of the drugs are known as cosolvents.

Hydrotropy
The term “hydrotropy” has been used to increase in aqueous solubility of various poorly water soluble compounds. Concentrated solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been used to enhance the aqueous solubility and dissolution of a large number of drugs.

Use of surfactant
Surfactants are amphipathic in nature, i.e. they have polar end (the circular head) and non-polar end (the tail). When a surfactant (e.g. Tween-80, sodium lauryl sulphate, polyethylene glycol, propylene glycol, polyvinyl pyrrolidone K30) is placed in water, it forms micelles. A non polar drug will partition into the hydrophobic core of the micelle and the polar head will solubilize the complex.

Functional polymer technology
Functional polymer improves the rate of dissolution of poorly soluble drugs by ignoring the lattice energy of the drug crystal, which is the main obstacle to rapid dissolution in aqueous media. The polymers used in this method are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly. The resultant complex, which is known as, “resinate”, can be formulated as a suspension, dry powder or tablet. The functional polymers are DUOLITETM AP 143 which is a cation exchange resin and AMBERLITETM IPR 69 which is anion exchange resin [16].

Porous microparticle technology
In this technology, the poorly water soluble drug is embedded in a microparticle having a porous, water soluble matrix. When such preparation mixed with water, the matrix dissolves, wetting the drug and thereby leaving a suspension of rapidly dissolving drug particles.
Controlled precipitation technology
In this process, the drug is first dissolved in a water miscible carbonic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water causing precipitation of the drug in the form of micro-crystals.

Solid Dispersions [17]
Two areas of pharmaceutical research primarily focus on improving the oral bioavailability of active agents by enhancing solubility and dissolution rate of poorly water-soluble drugs or by enhancing permeability of poorly permeable drugs.

Solid dispersion is defined as the dispersion of one or more active hydrophobic ingredients in an inert hydrophilic carrier at solid state and is prepared by melting (fusion), solvent, melting solvent method. The product formed contains different components i.e. a hydrophilic matrix and a hydrophobic drug.

When the solid dispersion comes in contact with the aqueous medium, the inert carrier dissolves thereby releasing the drug, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug.

Advantages of Solid Dispersion [8]
- Solid dispersion results in particle size reduction and thus the surface area increased and increased dissolution rate is attained. Hence bioavailability is improved.
- The carrier/polymer used in the solid dispersion plays an important role in improving the wetting of the particles. Improved wetting results in increased solubility thus improving the bioavailability.
- In solid dispersion, drugs are presented in amorphous form which increases the solubility of the particles.

Disadvantages of Solid Dispersion [18]
- Major disadvantage is their instability. They show changes in their crystalline state and a decrease in dissolution rate with ageing.
- Temperature and moisture may deteriorate solid dispersions more than its physical mixtures.
- Difficulty in handling because of tackiness.

Classification of Solid Dispersions [10]
First generation solid dispersions
The first description of solid dispersions was given by Sekiguchi and Obi in 1961 which showed that formulation of eutectic mixtures improved the rate of drug release which in turn increases the bioavailability of poorly aqueous soluble drugs [19]. Later, Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. These solid dispersions have the disadvantage of forming crystals, which are more thermodynamically unstable and did not release the drug as quickly as amorphous ones.

Second generation solid dispersions
It was noticed in the late sixties, that solid dispersion with drug in the crystalline state is not as effective as amorphous because they are thermodynamically stable therefore, second generation of solid dispersions are introduced having amorphous carriers instead of crystalline.

Third generation solid dispersions
Dissolution profile of third generation solid dispersions could be increased by using carriers having surface activity and self-emulsifying characteristics. The carrier may be a surfactant carrier or a mixture of amorphous polymers and a surfactant. The third generation solid dispersions stabilize the solid dispersions, increase the bioavailability of the poorly soluble drugs and reduce recrystallisation of drug. Surfactants have been added to stabilize the formulations, thus avoiding drug recrystallization and increasing their solubility.

Methods of Preparation of Solid Dispersions [20-22]
Various methods used for preparation of solid dispersion system. These methods are given below:
1. Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomeration Process
7. The use of surfactant
8. Electrospinning
9. Super Critical Fluid (SCF) technology

Melting or fusion method
In this method a physical mixture of the drug and a water soluble carrier is prepared, by heating it directly until it melts. The final cooled solid mass that is obtained is crushed, pulverized and sieved. However substances either the drug or the carrier may decompose due to high temperature during the melting process. To overcome this problem, heat the mixture in a sealed container or under vacuum or in the presence of inert gases like nitrogen. The advantage of this method is its simplicity and economical nature.

Solvent (evaporation) method
In this method physical mixture of the drug and the carrier is dissolved in common solvent and is evaporated to obtained a clear solvent free film. The main advantage is that the thermal decomposition of the drug or the carrier can be prevented because the organic solvents require a low temp for evaporation. The disadvantage in this method is difficulty in removing the organic solvent and higher cost of preparation.

Melt evaporation method
This method involves dissolving the drug in an appropriate liquid solvent and then incorporating the solution formed directly into the melt of polyethylene glycol which is evaporated to obtain a clear solvent free film. This method is a combination of both fusion and solvent evaporation method.

Melt extrusion method
Using twin screw extruder, the drug/carrier mix is simultaneously melted homogenized and extruded and shaped in different forms such as tablets, granules, pallets, powder etc. The method is applicable for thermolabile drugs as the mixture of the drug and carrier is subjected to elevated temperature for about 1 min.

Lyophilization
It is a phenomenon of transfer of heat and mass from and to the product. It is an alternative technique to solvent evaporation in which molecular mixture technique is used...
where the drug and carrier is dissolved in common solvent, frozen and sublimed.

**Melt Agglomeration technique**

In this technique binder is use as carrier. There are two method of preparation of solid dispersing, first is by spraying the drug on melted binder plus excipients and other one is melting of binder drug and exipient above the melting temperature of binder used. This technique is advantageous in homogenous mixing of drug but larger particle size cause densification and fines cause adhesion of mass.

**Electrosprinning method**

In this method electric force is used to withdraw a nano size fibre thread from the polymer sol/polymer melt. This a combination of solid dispersion with nanotechnology used in polymer industry. Stream of Polymer solution /melt is subjected to electric force (5 to 30kv) which cause body of the liquid becomes charged, and electrostatic repulsion counteracts the surface tension. This made a strong cohesive force between the particle or droplets of polymer and a stream of fibre is formed. Then thinning and stretching of fibre to nano diameter is done by using whipping process called electrostatic repulsion lead to formation of uniform nano size fibre. This process depends on the rate of feeding surface tension and electric force used.

**Supercritical fluid technology**

SCF is a substance above its critical point. Critical point represents the highest temperature and pressure at which the substance exists as vapour and liquid in equilibrium. In this method SCF is used to form solid dispersion of insoluble material/polymer with drug cause increase in dissolution property. It is superior over conventional technique(spray drying, hot melt etc.), as in this technique SCF carbon dioxide is mainly used which cause very rapid precipitation of solid mixture, giving no time for separation of drug and polymer in preparation of solid dispersion. It form very stable small particle with higher surface area for good flow and low organic solvent residual. In recent Solid dispersion of carbamazepine with PEG-4000 are made using SCF carbon dioxide in precipitation vessel, resulting in formation of carbamazepine with increase rate and extent of dissolution with low solvent residual & improved bioavailability.

**Criteria’s for Mouth Disintegrating Drug Delivery System**

[23]

Mouth dissolving tablets should

- Not require water for its administration and it should dissolve or disintegrate in the mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Be compatible with taste masking.
- Be transportable without friability concern.
- Leave minimal or no residue in the mouth after its oral administration.
- Exhibit minimum sensitivity to environmental conditions such as humidity and temperature.
- Permit the manufacturing of tablet using conventional processing and packaging at low cost.

**Salient Features of Mouth Dissolving Drug Delivery System**

[24]

- Ease of administration to patients who refuse to swallow a tablet such as, paediatric, geriatric patients and psychiatric patients.
- Water not needed to swallow the dosage form, which is highly convenient feature for patients who are roaming/travelling and do not have immediate access to water.
- Rapid disintegration and thus dissolution and absorption of drug which may produce quick onset of action.
- Good mouth feel property helps to change the basic view of medication as “bitter pill”, particularly for paediatric patients.
- Various drugs are absorbed from the mouth (buccal/sublingual cavity), pharynx and oesophagus as the saliva passes down into the GIT; in such cases bioavailability of drugs is increased.
- Pregastric absorption can result in improved bioavailability and as a result low dose required and improved clinical performance through a reduction of unwanted effects.

**Techniques for Preparing Mouth Dissolving Tablets**

[23,24]

**Freeze Drying**

Freeze drying a process in which water is sublimated from the product after freezing. Freeze dried forms exhibit more rapid dissolution than other available solid forms. The lyophilization process produces 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 because of high cost of the equipment and processing. Other major disadvantage of the final dosage forms is lack of physical resistance in standard blister packs.

**Sublimation**

Porous tablets which show good mechanical strength and dissolve quickly have been developed. Inert solid ingredients (ex. 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 produces a porous structure. Compressed tablets containing mannitol and camphor prepared by sublimation technique. Such tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use.

**Moulding**

Tablets produced by moulding are solid dispersions. Physical forms of the drug in the tablets depend on whether & to what extent it dissolves in the molten carrier. The drug can exist as separate particles or microparticles dispersed in the matrix. It can dissolve completely in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles remain 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, in general made from water soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the
moulded tablet usually occur during handling and opening of blister packs.

**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 has been employed by Allen and Wang, to prepare fast dissolving tablets.

**Mass Extrusion**
Mass Extrusion involves softening the active blend by 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 or produce tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste and make them palatable.

**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 this compression. Also high doses can be administered and final weight of tablet can easily exceed that of other production methods. Such tablet’s disintegration and dissolution depends on single or combined action of disintegrants & its concentration, water soluble excipients and effervescent agent. Disintegration is majorly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required for instant release tablets. As result, 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 packs may due to insufficient physical resistance.

**References**

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