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MOUTH MELT TABLETS-A NOVEL APPROACH IN DRUG DELIVERY SYSTEM

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ABSTRACT

Mouth melt tablets as the name implies that these tablets dissolve or disperse or combined effect of both within the oral cavity. The duration for disperse or dissolve is within few seconds without the use of water and as shows rapid onset of action with better patient compliance. Among other conventional dosage forms, Mouth melt tablets are one of the best options in emergency cases where the patient's survival is most important. It is one of choice of dosage form for geriatric and pediatric patients. Various technologies are used for the formulation as, Spray drying, Freeze drying, Tablet moulding technology depends on drug and excipients characteristics.

KEYWORDS: Tablets, Freeze drying, Spray drying, Water, Excipients.

INTRODUCTION

Oral Drug delivery is the safest, convenient and most economical method of drug delivery having the highest patient compliance. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules, the administration of drug is difficulty in swallowing leading to patient non-compliance particularly in case of pediatric and geriatric patients.[1] A study showed that 28% out of 1567 patients experience difficulty in swallowing tablets due to their (tablet's) large size.[2]

Recently more research is done on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients. Thus, a new delivery system known as oral fast dissolving/disintegrating (FDDS)/melt-in-mouth tablets is gaining importance. This type of oral dosage forms dissolve rapidly in saliva and can be swallowed

without the need of water. Elimination of bitterness is an important criteria for formulation of mouth dissolving tablets.

Mouth Dissolving Tablets are of two types i.e. buccal and sublingual tablets. These two classes of tablets are intended to be held in the mouth where they release their drug contents for absorption directly through the oral mucosa. These tablets are usually small and somewhat flat and are intended to be held between the cheek and teeth or in the cheek pouch (buccal tablets), or beneath the tongue (sublingual tablets).[3]

Drugs administered by this route are intended to produce systemic drug effects, and consequently, they must have excellent absorption properties through the oral mucosa. Drug absorption from the oral mucosa into the bloodstream that leads directly to the general circulation while from the gastrointestinal tract also leads to the mesenteric circulation which connects directly to the liver via the portal vein. Such type of formulation avoids first-pass metabolism. The oral route of administration from these two classes of tablet dosage form thus offers several possible advantages: The gastric environment, where decomposition may be extensive (for certain steroids and hormones), can be avoided by drugs that are well absorbed in the mouth. A more rapid onset of drug action occurs than for tablets that are swallow. The first-pass effect and for certain drugs (e.g., methyltestosterone) associated nausea can be avoided.[3]

Buccal and sublingual tablets must be formulated with blend of excipients which do not stimulate salivation. This reduces the fraction of the drug that is swallowed rather than being absorbed through the oral mucosa. In addition, these tablets should be designed not to disintegrate but to slowly dissolve, typically over a 15 to 30 min period, to provide effective absorption.[3]

Fast dissolving tablets (FDTs), upon admitted into the mouth, dissolve in the absence of additional water and ensure easy administration of active pharmaceutical ingredients.

The time for disintegration of orally disintegrating tablets is generally considered to be less than one minute although patients can experience actual oral disintegration times that typically range from 5-30 sec.[3]

In order to allow such tablets to dissolve in the mouth, they are made-up of either very porous and soft- moulded matrices or compressed into tablets with very low compression force

making them friable and/or brittle usually difficult to handle, often requiring specialized peel-off blister packaging.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

All the fast-dissolving tablets approved by FDA are classified as Oro dispersible tablets. The European Pharmacopoeia defines the term "orodisperse" as a tablet that can be placed in the mouth where it disperses rapidly before swallowing.[2]

The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."[4]

When fast dissolving tablets are placed in oral cavity, saliva quickly penetrates into the pores causing swelling and subsequent rapid disintegration of the tablet.
Hence, the basic approaches to develop MDTs include:[2]

- Maximizing the porous structure of the tablet matrix.
- Incorporating the appropriate disintegrating agent(s).
- Using highly water-soluble excipients in the formulation.

The basic approach used in the development of the fast-dissolving tablet is the use of super disintegrants, e.g. croscarmellose sodium, sodium starch glycolate and crospovidone. Another approach used in developing MD tablets is maximizing pore structure of the tablets.[5]

Orally disintegrating tablets are characterized by high porosity, low density and low hardness.[6]

There are three methods for addition of disintegrates into the formulation i.e. intra-granular (Internal addition), extra-granular (External addition) and partly intragranular and extra-granular additions.[1]

Fast dissolving tablets are prepared by various techniques such as direct compression, solid dispersion, molding, spray drying, freeze drying and sublimation. The simple process and cost effectiveness of direct compression process prefer over other processes.[1]

Mouth Melt Tablets (MMT)

Characteristics of mouth melt tablets[1,2]

They should:

- Not require water to swallow and should melt at body temperature in the mouth within a few seconds.
- Allow high drug loading.
- Be compatible with taste masking and other excipients.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.
- Allow the manufacture of tablets using conventional processing and packaging at low cost.

Salient features of mouth melt tablets[2]

1) MMT provides an ease of administration to the patients who cannot swallow e.g. elderly, stroke victims, bedridden, those affected by renal failure, pediatric, geriatric & psychiatric patients.
2) These dosage forms provide rapid melting, dispersion, dissolution and absorption of the drug leading to quicker onset of action.
3) MMT provides pregastric absorption resulting in improved bioavailability of the drug thus reducing the effective dosagic concentrations and dosing frequency.
4) No chance of temperature-based degradation as drying is not required.
5) These dosage forms provide new business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
6) These drug delivery systems are beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing where an ultra-rapid onset of action is required.
7) MMT are stable on storage for longer duration of time as stored at low temperature.

8) MMT can be taken while traveling without need of water.

Advantages over limitations of mouth dissolving tablets

- The MDT's usually have insufficient mechanical strength and hence, careful handling is required while mouth melt tablets, showed better hardness on storage.
- The MMT's may leave unpleasant taste and/or grittiness in mouth if not formulated properly while mouth melt tablets have a minimum amount of water insoluble matter.

Excipients used in mouth melt tablets[3,4,5]

The role of excipients is very important in the formulation of mouth melt tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of active principles, except some that require masking agents.

Bulking materials

Contribute functions of a diluents, filler and cost reducer. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol and DCL (direct compressible lactose) for higher aqueous solubility and good sensory perception. Bulking agents are added in the range of 10% to about 50% by weight of the final composition.

Anti-tackifier: It is an essential excipient, provides unstickiness and decreases the hygroscopicity. It can further assist in making such tablets more palatable after they melt in the mouth.

Flavours and Sweeteners: They make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose.

Meltable polymers: PEG's and blend of PEG.

Techniques used for the preparation of mouth melt tablet

Melt granulation technology had been developed for the preparation of oral dissolving drug delivery system, chosen for mouth melt formulation as follows:

Melt granulation[11]

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated using a molten liquid as a binder (meltable binder) which remains as a constituent of the formulation. This approach to prepare mouth melt tablet with sufficient mechanical integrity involves the use of a hydrophilic polymer (Superpolysylate, PEG-6-stearate). Superpolysylate is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it not only acts as a binder and increases the physical resistance of tablets but also aids disintegration of tablets as it melts in the mouth and solubilises rapidly leaving no residue.

The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

Agglomerates can be classified into two types: granules and pellets.

1- Granules are irregularly shaped agglomerates which have rather a wide size distribution, typically within the range of 0.1-2 mm.
2- Pellets are spherical agglomerates with a narrow size distribution, within the range of 0.5-2 mm.

Most common method employed for characterization of melt agglomerates is the determination of mean agglomerate size and size distribution by sieving.

In-vitro dissolution studies have been conducted to examine the drug release characteristics of melt agglomerates. **El-Shanawany and Voinovich et. al**, found that in-vivo drug release attributes of melt agglomerates were in accordance with the in-vitro findings. Nonetheless, a quantitative relationship between the in-vivo and in-vitro performances of melt agglomerates is still generally lacking.

Another important feature of melt agglomerates is their performance stability during storage. It was found that the melt agglomerates could maintain their dissolution profile after a year of storage at 25ºC and 60% relative humidity e.g.: release of sulfamethazine from tablets made up of melt granules remained unchanged after 2 years of storage at 25ºC in closed containers. On the basis of the 1meltable nature of agglomerates, stability testing is preferred to be

conducted at an appropriate choice of storage temperature which will not bring about marked alterations to the physicochemical state of the agglomerates.

Mechanism of melt agglomeration

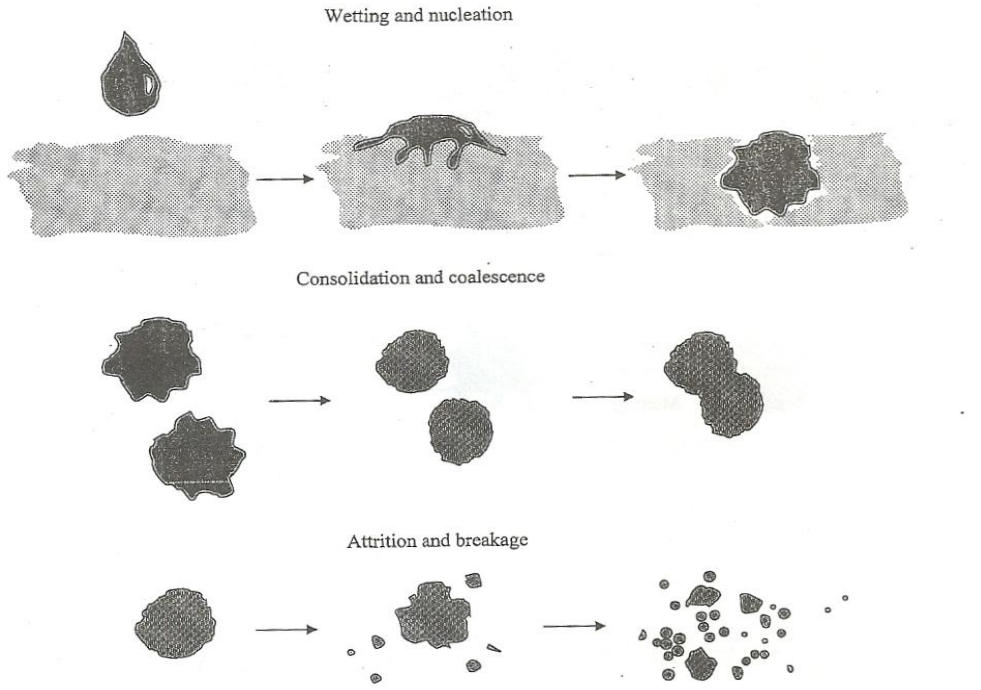

Fig. 1.1: A recent approach in describing the agglomeration mechanism.

The growth process of melt agglomerates is dependent on the interplay between the size enlargement and size reduction processes. The likelihood of an agglomerate to grow in size or experience breakages is a result of the balance between externally applied mechanical forces and agglomerate strength. The agglomerates will grow in size if they have sufficient strength to withstand the impact of externally applied forces or vice versa. The strength of agglomerates is affected by the relative magnitude of capillary, frictional and viscous forces. The capillary forces aid agglomerate consolidation by pulling the solid particles together while the viscous and frictional forces resist both consolidation and dilation of the solid particle assembly.

The process of agglomeration consists of a combination of three phases: wetting and nucleation, consolidation and growth, together with the steps of attrition and breakage.

Wetting and Nucleation

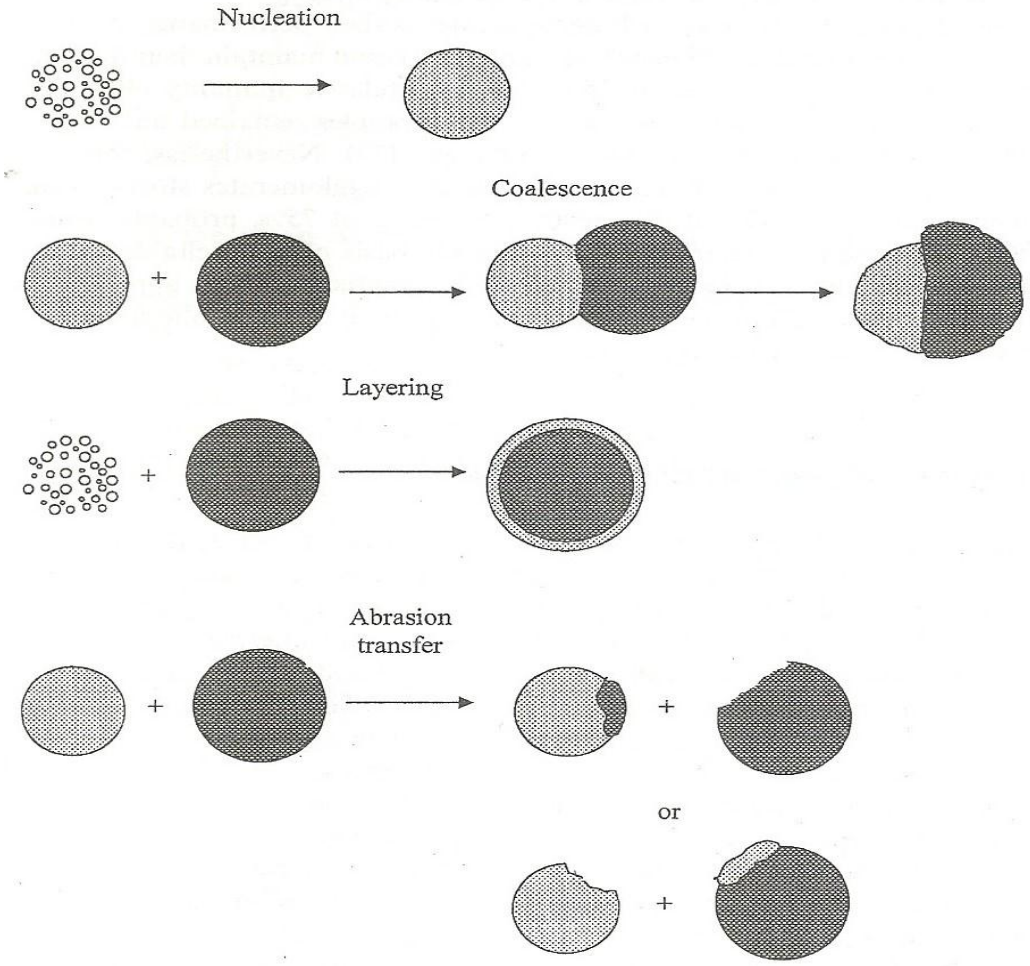

Fig. 1.2: Elementary agglomerate growth mechanisms.

Nucleation is the initial phase of agglomeration in which nuclei or small agglomerates of loose and porous structure are formed after the primary particles are wetted by a binding liquid droplet. The primary particles are bound by liquid bridges in the pendular state. The degree of liquid saturation of an agglomerate can be increased either by continuous addition of liquid or through the consolidation of the agglomerate. Two nucleation mechanisms, namely immersion and distribution, are proposed by **Schaefer and Mathiese**, based on the process of melt agglomeration. The dominance of either mechanism in the nucleation process of melt agglomeration is a function of the ratio between the sizes of primary particles and molten binder droplets.

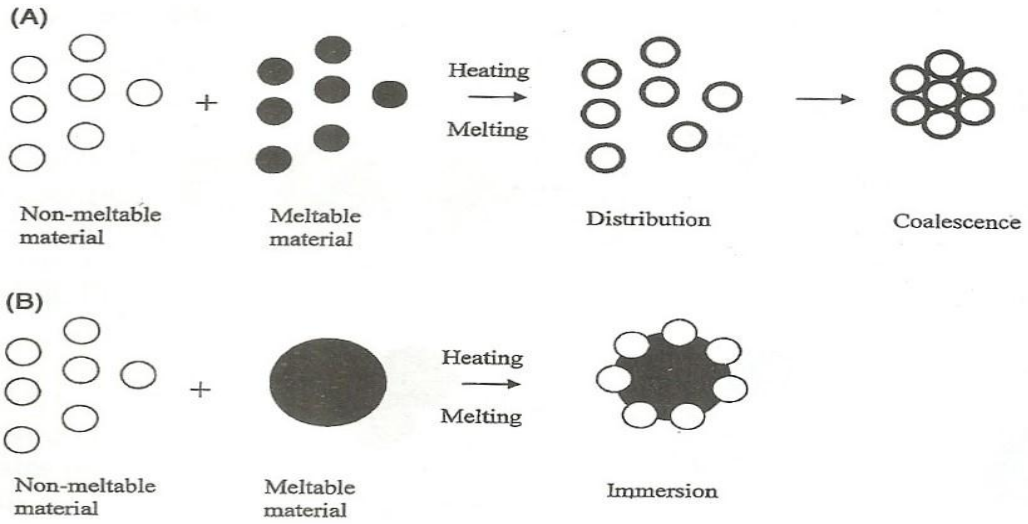

Fig. 1.3: Modes of nucleation mechanism: (A) distribution and (B) immersion.

Nucleation by immersion occurs when the size of the molten binder droplets is greater than that of the fine solid particles. Immersion proceeds by the deposition of fine solid particles onto the surface of molten binder droplets. The propensity of nucleation by immersion method is promoted by large binder droplet size, high binder viscosity and low shearing forces that reduce the opportunity for molten binder droplets to break down, thus keeping their size comparatively large and several times the size of the fine solid particles.

In nucleation by distribution method, a molten binding liquid is distributed onto the surfaces of fine solid particles. The nuclei are formed by the collision between the wetted particles. The formed nuclei have a loose structure with entrapped air unlike those produced by the immersion method. Generally, small binder droplet size, low binder viscosity and high shearing forces are favorable conditions for nucleation by the distribution method.

The nucleation phase is characterized by the disappearance of fines, as a consequence of coalescence between the wetted primary particles or the primary particles with the formed nuclei. The resultant nuclei would undergo consolidation under the impact of the externally applied mechanical forces and acquire sufficient strength to resist further breakdown by impact forces and will be able to grow into bigger agglomerates.

Consolidation and Growth

The probability of successful fusion between the collided nuclei is dependent on the liquid saturation state of nuclei. During the process of agglomeration, the agglomerates are consolidated by the agitation forces. The reduction in agglomerate pore size and number

promotes the migration of binding liquid from agglomerate core to surfaces, thus enhancing the surface plasticity and propensity of agglomerate growth by coalescence. The rate and extent of consolidation of an agglomerate is governed by interparticulate frictional, capillary and viscous forces. The interparticulate frictional and viscous forces resist the consolidation process of agglomerates.

Attrition and Breakage

Attrition and breakage refer to the phenomenon of agglomerate fragmentation in the dry and wet states respectively. In melt agglomeration, the formed agglomerates are solidified by tray cooling to ambient temperature without the need for drying by a tumbling process. Consequently, breakage is known to have a more essential role in affecting the resultant properties of the melt agglomerates during the agglomerative phase.

CONCLUSION

Mouth melt tablets has s solved most of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of mouth melt tablets, which in turn prolongs the patent life of a drug. Due to the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more useful.

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