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ORAL DISSOLVING TABLETS: A REVIEW

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ABSTRACT

The new dosage form which is convenient in administration and manufacturing should free from side effects and should exhibit immediate release with better patient compliance and enhanced bioavailability. Tablets are the most widely accepted dosage forms in oral drug delivery system due to its numerous advantages. But beside the advantages there a few disadvantages like sudden exposure of allergies, mental disability, motion sickness, unconsciousness, lack of water etc. In order to overcome such difficulties new drug delivery systems like fast dissolving tablets were developed. As this dosage form shows a very rapid rate of disintegration when they placed over the tongue without aid of water they became most popular and convenient dosage forms for geriatrics and paediatrics with improved patient compliance.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration, the drug is well absorbed as the food stuffs ingested daily.[1] Oral route of drug administration has wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular and most preferred route due to its advantages because of ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules. One important drawback of these dosage forms for some patients however is difficult to swallow.2The development of Oro Dissolving Tablets (ODT) covers all these drawbacks of conventional dosage forms. In recent market study indicated, the ODT had most preferred dosage form than conventional tablets and capsules. Oro Dissolving Tablets (ODT) is those when put on tongue dissolve instantaneously releasing the drug which disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage forms.

Their growing importance was underlined recently when European pharmacopoeia adopted the term ―Oro Dissolving Tablet, as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes.Oro dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, fast dispersible tablets, porous tablets, quick dissolving tablets etc. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pre-gastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population suggested Oro Dissolving Tablets today. These people eventually will experience deterioration of their physiological and physical abilities.

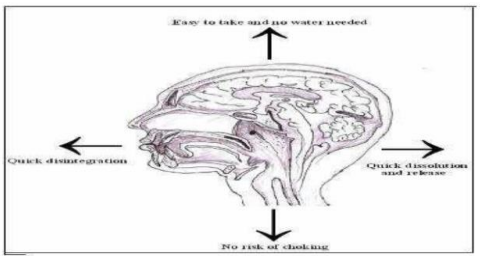

Fig no.1 Advantages of Oro dissolving tablet

Orally dissolving tablet
↓
Placed in Mouth
↓ Rapiddrug dispersion/dissolution in saliva
↓
Pre-gastric absorption
↓
Avoid first pass metabolism
↓
Increase in bioavailability
↓
Faster onset of action

1.1 Criteria for Oro dissolving Drug Delivery System:

- The tablets should not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing.

1.2 Benefits of Oro Dissolving Tablets

1. Convenience of administration and accurate dosing as compared to liquids.

2. No need of water to swallow the dosage form, which is highly convenient especially for patients who are travelling and do not have immediate access to water.

3. Good mouth feel property of these tablets helps to change the basic view of medication as "bitter pill", particularly for paediatric patients.

4. Rapid dissolution and absorption of drug, which may produce quick onset of action.

5. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.

6. Ability to provide advantages of liquid medication in the form of solid form.

7. Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical

performance through a reduction of unwanted effects.

8. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of tablets.

1.3 Limitations of Oro dissolving tablets

1. The tablets may leave unpleasant taste or grittiness in mouth if not formulated properly. The tablets usually have low hardness. So, they are friable and/or brittle and are difficult to handle. They often require specialized peel-off blister packaging and careful handling required.

2. Delivery of drug from the fast dissolving formulation would not expect to avoid first pass metabolism since the unit disintegration rapidly and the drug would be swallowed.

1.4 Methods of preparing orally dissolving tablets

Many techniques have been reported for the formulation of Oro dissolving tablets or Oro dispersible tablets.

1.4.1 Freeze drying / lyophilisation.
1.4.2 Tablet Moulding.
1.4.3 Spray drying.
1.4.4 Sublimation.
1.4.5 Direct compression.
1.4.6 Mass extrusion.

1.4.1 Freeze-Drying or Lyophilisation.[7]

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability.

1.4.2 Tablet Moulding[8]**:** Moulding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30○C under vacuum. The mechanical strength of moulded tablets is a matter of great concern. Binding agents,which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophilisation technique, tablets produced by the moulding technique are easier to scale up for industrial manufacture.

1.4.3 Spray Drying[9]**:** In this technique, gelatine can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or cross carmellose or cross povidone are used as

superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate&croscarmellose sodium and acidic ingredient (citricacid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

1.4.4 Sublimation[10, 11]: To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane; benzene can be used as pore forming agents.

1.4.5 Direct Compression[12]: Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially super disintegrants and sugar based excipients.

In many orally dissolving tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Mechanism of Super disintegrants:

There are four major mechanisms for tablet disintegration as follows:

a. Swelling: Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

b. Porosity and capillary action (Wicking): Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. The wicking and swelling process of disintegration is shown in Fig 2.

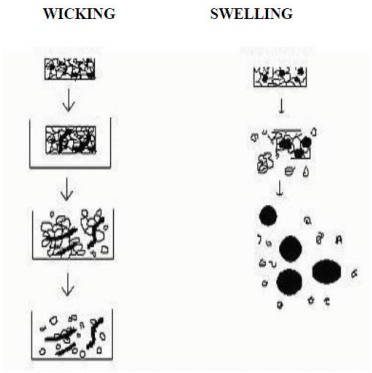

Fig no.2 Disintegration by wicking and swelling process

C. Due to disintegrating particle/particle repulsive forces: Another mechanism of disintegrants attempts to explain the swelling of tablet made with non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

d. Due to deformation: During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied. Disintegration of tablets by deformation and repulsion is shown in Fig no. 3.

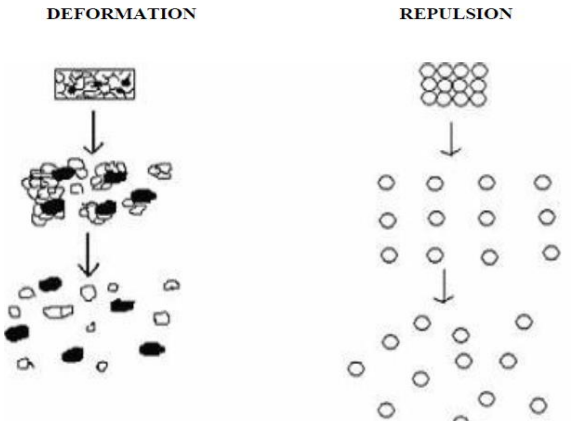

Fig.no3 Disintegration by deformation and repulsion process

1.4.6 Mass-Extrusion: This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

1.5 Important Patented Technologies for Oro Dissolving Tablets

1.5.1Zydis technology [13,14] :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 material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatine, 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 while 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.

1.5.2 Durasolv technology[15]: Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler 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 product requiring low amounts of active ingredients.

1.5.3Orasolv technology [16]: 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 produce the tablets. The tablets produced are soft and friable.

1.5.4 Flash dose technology[17]: Flash dose technology has been patented by Fuisz. Nurofenmeltlet, 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 consist of self-binding shear form matrix termed as floss. Shear form matrices are prepared by flash heat processing.

1.5.5 Wow tab technology[18, 19]

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. "WOW means WithOut Water". In this process, combination of low mouldability saccharides and high mould ability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide e.g. lactose, glucose, and mannitol and granulated with a high mouldability saccharide e.g. Maltose, Oligosaccharides and compressed into tablet.

1.5.6 Flash tab technology [20]: Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of microcrystals. Drug granules may be prepared by using the conventional techniques like coaservation, micro encapsulation and extrusion spheronisation.

1.6 Methods of taste masking[21]

An ideal taste masking process should have the following properties

1) Involve least number of equipment's and processing steps.
2) Require minimum number of excipients for an optimum formulation.
3) No adverse effect on drug bioavailability.
4) Require excipients that are economical and easily available.
5) Least manufacturing cost.
6) Can be carried out at room temperature.
7) Require excipients that have high margin of safety.
8). Rapid and easy to prepare.

Various methods are available to mask undesirable taste of the drugs. Some of these are as given below.

1.6.1 Coating of drug particles with inert agents: Coating is an extremely useful technique for number of applications in the pharmaceutical field profile. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH would be an acceptable alternative for taste masking. Various inert coating agents like starch, povidone, gelatine, methylcellulose, ethyl cellulose etc. are used for coating drug particles. One of the most efficient methods of drug particle coating is the fluidized bed processor.

1.6.2 Taste masking by formation of inclusion complexes: In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Beta-cyclodextrin is most widely used complexing agent for inclusion type complexes.

1.6.3 Molecular complexes of drug with other chemicals: The solubility and absorption of drug can be modified by formation of molecular complexes.

Consequently lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug. It is reported that caffeine forms complexes with organic acids that are less soluble than xanthene and as such can be used to decrease the bitter taste of caffeine.

1.6.4 Solid dispersion system: Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Solid dispersion is also called as co-precipitates for those preparation obtained by solvent method such as co-precipitates of sulphathiazale and povidone. Also using them as absorbents on various carriers may increase the stability of certain drugs.

1.6.5Microencapsulation:
Microencapsulation is a process by which solids, liquids or even gases may be enclosed in microscopic particles formation of thin coatings of wall material around the substances. A well designed drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having particle size less than 200μm. Microspheres received much attention not only for prolong release, but also it is reliable means to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest without untoward effect.

1.6.6 Pro-drug: A pro-drug is a chemically modified inert drug precursor, which up on bio-transformation liberates the pharmacologically active parent drug.

1.6.7 Ion Exchange Resin: Another popular approach in the development of taste masking is based on ion exchange resin. Ion exchange resins are solid and suitably in soluble high molecular weight poly electrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stoichiometric with the displacement of one ionic species by another. Ion exchange resins like Amberlite CG 50 were used for taste masking of pseudo ephedrine in the chewable Rondec decongestant tablet.

Summary

Orally Dissolving Tablets are new drug delivery in the field of tablet dosage form which can dissolve/disperse/disintegrate in the saliva without the need of water. The advantages of ODT are improvement of patient compliance, rapid onset of action, increased bioavailability and good stability which make the tablet as a popular dosage form of choice current market. Oro dissolving tablets are the inventive dosage forms which are designed for rapid disintegration in saliva without water. Orally dissolving tablet is growing in an exceedingly positive manner because of its several potential advantages over conventional dosage forms and its usage by geriatrics and pediatrics. They show higher bioavailability over conventional dosage forms. Hence oro dissolving tablets became the most popular choice over conventional dosage forms around the world.

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