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ORAL DISPERSIBLE TABLETS - AN OVERVIEW

V. Lavakumar*[1], L. Divya[2], C. Sowmya[2], M. Niranjanbabu[2], V. Rajasekar reddy[2], A. Srilakshmi[2]

[1*]Department of Pharmaceutics, Seven Hills College of Pharmacy, Tirupathi, Andhra Pradesh, India.
[2]Department of Pharmaceutics, Omer EL Mukhtar University, Al-Beida, Libya.

ABSTRACT

Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Recent advances in technology prompted researchers and scientists to develop oral disintegrating tablets with improved patient convenience and compliance. Oral dispersible tablets are solid unit dosage form which dissolve or disintegrate rapidly in the mouth without water or chewing. Novel Oral dispersible tablet technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatric, geriatric and psychiatric patients who have difficulty in swallowing (Dysphagia) conventional tablet and capsules. Technologies used for manufacturing of Oral dispersible tablets are either conventional technologies or patented technologies. This review depicts the various aspects of Oral dispersible tablet formulation; superdisintegrants and technologies developed for Oral dispersible tablets, along with various drugs explored, evaluation tests and marketed formulations in this field.

KEYWORDS

Disintegration, Oral disintegrating tablets, Superdisintegrants and Dysphagia.

Author for Correspondence:
Lavakumar V,

Department of Pharmaceutics,

Seven Hills College of Pharmacy,

Tirupati, Andhra Pradesh, India.

Email: shcpresearch@gmail.com

INTRODUCTION

Oral route of administration is still continue to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular dosage form being tablets and capsules[1]. Even few of the drawbacks of these dosage forms like swallowing and some drugs resist comparison in dense compacts, owing to their amorphous nature or flocculant, low-density characteristics. Drugs with poor wetting, slow dissolution properties, intermediate to large dosage,

and optimum absorption in the gastrointestinal tract or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability. Bitter tasting drugs, drugs with an objectionable odor, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression.

The target population of these dosage forms is pediatric, geriatric, bedridden, developmentally disabled and the patients with persistent nausea or who are in traveling or who have little access to water[2]. Even many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy[3].

Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecule by formulation and to achieve better patient compliance. One such approach is 'mouth dissolving tablets[4], which disintegrate or dissolve in saliva and are swallowed without water as tablet disintegrate in mouth, this could enhance the clinical effect of drug through pregastric absorption from the mouth, pharynx, esophagus. This leads to an increase in the bioavailability by avoiding first pass liver metabolism[5].

Mouth dissolving is also called as orodispersible tablets, melt-in-mouth, fast dissolving tablet, rapimelts, porous tablets, quick dissolving etc. Their growing importance was underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablets" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. It is one of the fastest growing segments in the pharmaceutical market[6].

Desired Criteria for Mouth Dissolving Drug Delivery System[7, 8]

The tablets should

- Not require water to swallow, but is should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable with taste masking.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

Salient Features of Mouth Dissolving Tablet[9, 10]

- Ease of administration to patient who refuses to swallow tablets, such as pediatric, geriatric and psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improve clinical performance through a reduction of unwanted effects.

Techniques for Preparing Mouth Dissolving Tablets

Freeze Drying

A process in which water is sublimated from the product after freezing is called freeze drying. Freeze dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation[11-14]. However, the use of freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs. Scherer RP patented Zydis technology by employing freeze drying process for the preparation of mouth dissolving tablets on the basis of patents issued to Gregory et al. Jaccard and Leyder also

utilized lypholization to prepared orodispersible tablets of various drugs.

Moulding

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier and the remaining particles stay un-dissolved and dispersed in the matrix[15]. 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 posses great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs[16-18].

Sublimation

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in water[19-22]. Porous tablets that exhibit good mechanical strength and dissolved quickly have been developed. Inert solid ingredients (e.g., urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipient and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use.

Spray Drying

Spray drying can be used to prepare rapidly dissolving tablets. This technique is based upon a particulate support matrix that is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder[23]. This is then mixed with active ingredient and compressed into tablet. Allen and Wang have employed spray drying technique to prepare orodispersible tablets.

Mass Extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets[24, 25]. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

Direct Compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can accommodate and final weight of tablet can easily exceed that of other production method. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water-soluble excipients and effervescent agent[26,27]. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and/ or high friability and low hardness.

Patented Technologies for Mouth Dissolving Tablets

Zydis Technology

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

to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis unit during freeze drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

Shearform Technology

The shearform technology is based on preparation of floss that is also known as 'shearform matrix', which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystallized by various techniques to provide uniform flow properties and thus facilitate blending[22]. The recrystalized matrix is then blended with other tablet excipient and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipient can be blended with floss before carrying out recrystallization. The shearform floss, when blended with the coated or uncoated microspheres is compressed into flashdose or EZ chew tablets on standard tableting equipment.

Ceform Technology

In Ceform technology microspheres containing active drug ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a precision engineered and rapidly-spinning machine. The centrifugal force of the rotating head of ceform machine throws the drug blend at high speed through small, heated openings. The carefully controlled temperature of the resultant microburst of heat liquifies the drug blend to form a sphere without adversely affecting drug stability. The microspheres are then blended and/ or compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipient generates a unique microenvironment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance, such as enhancing solubility and stability. The microspheres can be incorporated into a wide range of fast dissolving tablets such as Flashdose, EZ chew, Spoon Dose, as well as conventional tablets.

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked and also contains effervescent 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 and packaged in specially designed pick and place system.

Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Company WOW means "without water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in theform of microcrystals. Drug microgranules may be prepared using the conventional technique like coacervation, microencapsulation and extrusion spheronization. All these processes utilized conventional tableting

technology[28]. Nowadays orodispersible tablets are gaining more and more importance in the market. Currently, these tablets are available in the market for many diseases; more is concentrated on analgesics and anti-pyretics. Research is in progress for anti-hypertensives, anti-emetics and anti-asthmatics.

Nanocrystal technology

NanoCrystal™ Fast dissolving technology provides for: Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix. Nano Crystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. This method avoids manufacturing process such as granulation, blending and tabletting which is more advantages for highly potent and hazardous drugs. For fast dissolving tablets, Elans proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase dissolution rate[27].

Evaluation of ODTs

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Hardness

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness test.

Friability

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

Wetting time and water absorption ratio

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure[29]. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio, *R* can be the determined according to the following equation.

$$R = 100 (Wa-Wb) / Wb$$

Moisture uptake studies

Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a dessicator over calcium chloride at 370C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Disintegration test

The time for disintegration of ODTs is generally <1min and actual the disintegration time that patients can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents.

Dissolution test

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher

Paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile[29, 30].

Patient counseling points for ODT

As pharmacist are ideal person to become familiar with recent technology advancement in novel dosage form, thus have opportunity to counsel the patient for effective treatment. Educating the patients about ODT can avoid any confusion and misunderstanding of this dosage form.

Counseling points to the patients include:

- Patients may mistake ODT for effervescent tablets, pharmacist need to be clearly told about the different between them. The cima technologies orosolv and durasolv use slight effervescence, patients may experience a pleasant tingling effect on the tongue.
- ODT need to be handled carefully because some of ODT developed may not have sufficient mechanical strength.
- Patients with dryness of mouth or with siogrens syndrome or who taking anticholengic drugs may not be suitable population for administering ODT. Although no water is needed to allow the drug to dispense quickly and efficiently but most technologies of ODT utilizes the body own salivation but decreased volume of saliva may slow down dissolution/ disintegration/ bioavailability of the product.
- Although chewable tablets have been in the market for long time, patients need to be counseled properly the difference between chewable and ODT tablets. ODT can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth and also for geriatric patients who have lost their teeth permanently.
- With the pharmacist counseling, intervention and assistance all of these patients who taking ODT could be more properly treated with greater convenience.

CONCLUSION

Orally disintegrating tablets have potential advantages over conventional dosage forms, with improved patient compliance, convenience, bioavailability and rapid onset of action. They are a very good alternative for drug delivery to geriatric and pediatric patients. They have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. As a result of the variety of technologies for its formulation, several commercial products are available in the market. Thus ODT has tremendous scope for being the delivery system for most of the drugs in near future.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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