

**Review article****Mouth dissolving tablets: A current review of scientific literature**

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ABSTRACT

The objective of this paper was to review the information about mouth dissolving tablets. Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Among them, mouth dissolving drug delivery systems (MDDDS) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life. MDDDS have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. This is seen to afflict nearly 35% of the general population and associated with a number of conditions, like parkinsonism, mental disability, motion sickness, unconsciousness, unavailability of water etc. To overcome such problems, certain innovative drug delivery systems, like 'Mouth Dissolving Tablets' (MDT) have been developed. These are novel dosage forms which dissolve in saliva within a few seconds, when put on tongue. Such MDTs can be administered anywhere and anytime, without the need of water and are thus quite suitable for children, elderly and mentally disabled patients. This article describes the existing techniques for fast dissolving oral preparation, highlights their manufacturing processes, evaluation parameters and future trends for these evolving forms. Such MDTs can be administered anywhere and anytime, without the need of water and are thus quite suitable for children, elderly and mentally disabled patients. The excipients that are currently used as well as those that are expected to be used for the future development of improved FDTs are described in the review paper.

1. Introduction

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration. Patient compliance is one of the most important aspects in the pharmacy practice. Now days, pharmacy companies are coming up with development of new drug delivery systems to ensure the delivery of the drugs to the patients efficiently and with fewer side effects. This objective led to the emergence of the concept of Mouth Dissolving Tablets. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films^[1]. These are also called melt-in-mouth tablets, repimelts, porous tablets, oro-dispersible, quick dissolving or

rapid disintegrating tablets, Mouth dissolving tablets, fast dissolving, rapid dissolve, fast melts, Effervescent Drug Absorption system, Orosolv, Zydis etc. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients^[2,3]. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients^[4,5]. Those who are traveling or have little access to water are similarly affected^[6,7]. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics⁸.

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Their growing importance was underlined recently when European pharmacopoeia adopted the term “Orodispersible 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. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrrolidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.

Recently Orally disintegrating (OD) tablet technology has been approved by United States Pharmacopoeia (USP), Centre for Drug Evaluation and Research (CDER). USFDA defined OD tablet as “A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”^[8].

2. Criteria for mouth dissolving drug delivery system^[9,10,11]

Choice of drug candidate

Suitable drug candidate for mouth dissolving tablet should posses;

- No bitter taste.
- Good stability in water and saliva.
- Dose should be low as possible.

Unsuitable drug candidate for mouth dissolving tablet should include;

- Short half-life and frequent dosing
- Drug having very bitter taste
- Required controlled or sustained release^[12].

Hurdless to develop rapidly disintegrating drug delivery systems

- Rapid disintegration of tablet.
- Avoid Increase in tablet size.
- Have sufficient mechanical strength.
- Minimum or no residue in mouth.
- Protection from moisture.
- Compatible with taste masking technology.
- Not affected by drug properties^[13].

Table No.1: Drugs to be promising in incorporated in fast dissolving tablets^[14]

Category	Drugs can be used
Analgesics and anti-inflammatory agents	Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenpropfen Calcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.
Anthelmintics	Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Ivermectin, Mebendazole, Oxarnniquine, Oxfendazole, Oxantel Embonate, Praziquantel, Pyrantel Embonate, Thiabendazole.
Anti-arrhythmic agents	Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate.
Anti-gout agents	Allopurinol, Probenecid, Sulphinpyrazone.
Anti-hypertensive agents	Amlodipine, Carvedidol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidii, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.
Anti-malarials	Amodiaquine, Chloroquine, Chlorproganil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate, Anti-Migraine Agents: Dihydroergotamine Mesylate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate.
Anti-muscarinic agents	Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine Butyl Bromide, Hyoscyarnine, Mepenzolate Bromide, Orphenadrine.

Anti-neoplastic agents and immunosuppressants	Aminogluethimide, Amsacrine, Azathioprine, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mithomycin, Mitatane, Mitozantrone, Procarbazine, Tamoxifen, Testolactone.
Anti protozoal agents	Benznidazole, Clioquinol, Decoquinol, Diiodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.
Anti-thyroid agents	Carbimazole, Propylthiouracil.
Anxiolytic, sedatives and hypnotics	Alprazolam, Amyobarbitone, Barbitone, Bentazepam, Bromazepam, Bromperidol, Brotizolam, Butobarbitone, Carbromal, Chlordiazepoxide.
Cardiac inotropic agents	Amrinone, Digoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin.
Coricosteroids	Beclomethasone, Betamethasone, Budesonide, Cortisone, Acetate, Desoxymethasone, Dexamethasone, Fludrocortisone Acetate.
Anti-parkinsonian agents	Bromocriptine Mesylate, Lysuride Maleate.
Gastro-intestinal agents	Bisacodyl, Cimetidine, Cisapride, Diphenoxylate, Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole.
Histamine H₂-receptor Antagonists	Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadine, dimenhydrinate, Flunarizine
Lipid regulating agents	Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol.
Local anaesthetics	Lidocaine
Neuro-muscular agents	Pyridostigmine
Nitrates and other anti-anginal agents	Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrat.
Opioid analgesics	Codeine, Dextropropoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine.
Oral vaccines	For Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera.

3. The need for development of FDTs^[15-16]

The need for non-invasive delivery system persist due to patients' poor acceptance of , and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

3.1. Patient factors

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H₂-blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water.

3.2. Effectiveness factor

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pregastric segments of GIT.

3.3. Manufacturing and marketing factors

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size. As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations. As examples, Eisai Inc. launched Aricept ODT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M (simvastatin ODT), a line extension of its block-buster, Zocor®, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2000⁴²⁴. Marketers build a better brand and company image when they offer a unique easier-to-take form that satisfies the need of an underserved patient's population^[17].

4. Advantages of mouth dissolving tablets^[18, 19, 20]

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients.
- Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
- Good mouth feel property of mouth dissolving drug delivery system helps to change the basic view of medication drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.

- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension^[21,22].

5. Concept of co-processing

Coprocessing is defined as combining two or more established excipients by an appropriate process^[23-24]. Co-processing is a process in which two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality price. Co-processing is interesting because the products are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within mini granules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and reliable. The randomized embedding of the components in special mini granules minimizes their anisotropic behavior. So, deformation can occur along any plane and multiple clean surfaces are formed during the compaction process. Thus, the use of the co-processed excipient combines the advantages of wet granulation with direct compression^[25]. Most important characteristics are binding and blending properties of the co-processed excipients, which must be better than those of a physical mixture of the starting materials. Cost is another factor to be considered in the selection of co-processed product. Coprocessing of excipient could lead to formation of excipients with superior properties compared with the simple physical mixture of their components or with individual components. A large number of coprocessed diluents are commercially available. The representative examples are ludipress, cellactose, and starlac. The use of coprocessing is a totally unexplored avenue in disintegrants. The widely used superdisintegrants are sodium starch glycolate, croscopovidone, and croscarmellose sodium. Like diluents each superdisintegrant has strengths and weaknesses. Sodium starch glycolate exhibits good flow (angle of repose G36°). The bulk density of croscopovidone and sodium starch glycolate is 0.4 and 0.756 g/cm³, respectively. Hence, if a physical mixture of superdisintegrants is used in high-speed tableting, the problem of segregation of the disintegrants may be encountered. One of the reasons for preparing the coprocessed superdisintegrant was to avoid the problem of segregation. A blend of swelling and wicking types of excipient may also prove to be efficient because the medium (usually water) required for swelling will be brought into the tablet more easily if a wicking (hydrophilic) type of superdisintegrant is also present^[26, 27].

6. Excipients commonly used in formulation of mouth dissolving tablets^[28, 29, 30, 31]

Mainly seen excipients in FDT are as at least one disintegrant, a diluent, a lubricant and optionally, a swelling agent, a permeabilizing agent and flavourings.

6.1. Role of super-disintegrants in mouth dissolving tablets^[32, 33, 34]

The basic approach in development of FDTs is use of disintegrant. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Disintegrants are agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule “slugs” into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix^[35]. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agents in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared. Disintegrants are an essential component to tablet formulations. The ability to interact strongly with water is essential to disintegrate function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrate action. A disintegrate used in granulated formulation processes can be more effective if used both “intragranularly” and “extragranularly” thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. However, the portion of disintegrate added intragranularly (in wet granulation processes) is usually not as effective as that added

extragranularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrate. Since a compaction process does not involve its exposure to wetting and drying, the disintegrate used intragranularly tends to retain good disintegration activity. Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. Super disintegrates are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the super disintegrant, whereas if concentration of super disintegrant is above critical concentration, the disintegration time remains almost constant or even increases.

6.2. Mode of addition^[36,37]

There are three methods of incorporating disintegrating agents into the tablet:

- (i). Internal addition (Intragranular)
- (ii). External addition (Extragranular)
- (iii). Partly internal and external.

Water penetration rate and rate of disintegration force development are generally positively related to disintegrate efficiency in nonsoluble matrix in a direct compression process drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet. A disintegrate used in this type of formulation, simply has to break the tablet apart to expose the drug substance for dissolution. The proper choice of disintegrate and its consistency of performance are of critical importance to the formulation development of such tablets^[38].

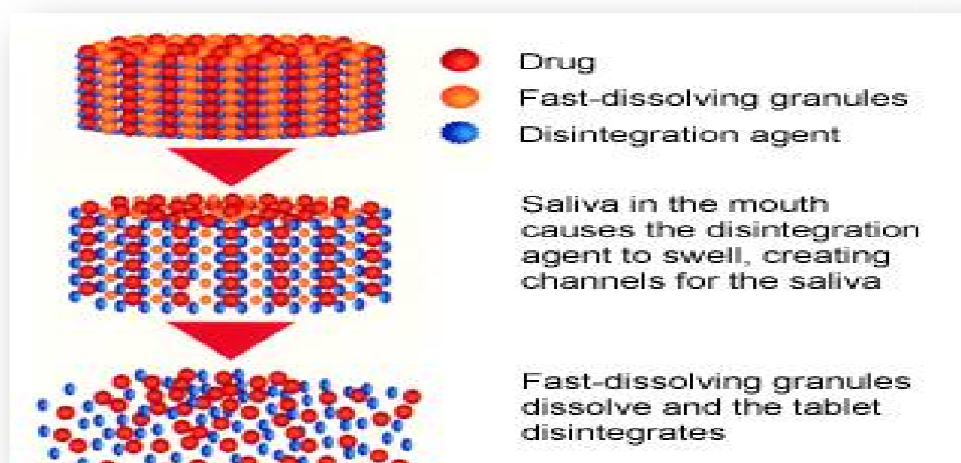


Fig 1: Mechanism of disintegration of mouth dissolving tablets

6.3. Mechanism of tablet disintegration^[39,40]

There are four major mechanisms for tablets disintegration as follow:

6.3.1. Swelling

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.

6.3.2. 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 /excipient 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.

6.3.3. Due to disintegrating particle/particle repulsive forces

This mechanism of disintegration attempts to explain the swelling of tablet made with 'nonswellable' disintegrants. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

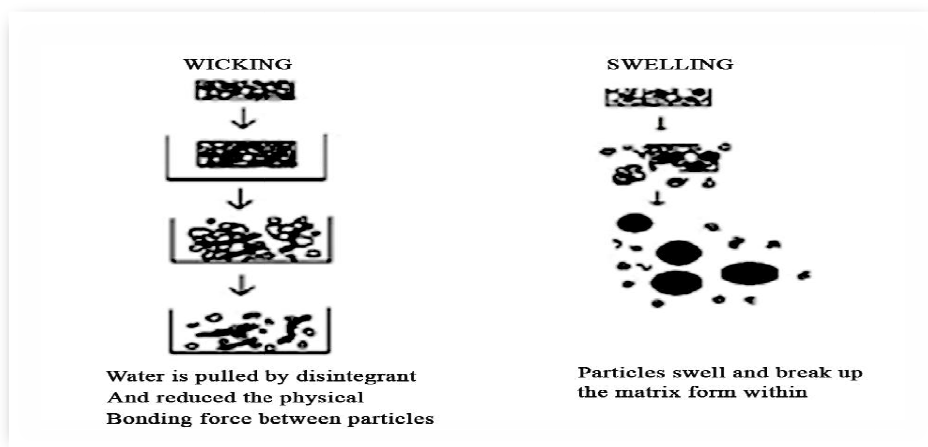


Fig: 2 Mechanism of Superdisintegrants: Porosity and capillary action (Wicking)

6.3.4. 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.

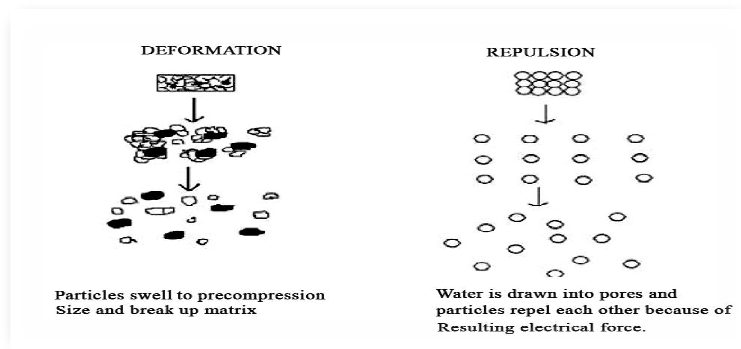


Fig 3: Steps involved in repulsion and deformation

6.3.5. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegratn attempts to explain the swelling of tablet made with non-swellaable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the

mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Factors affecting action of disintegrants^[41,42]

1. Percentage of disintegrate present in the tablets
2. Type of excipients present in the tablets
3. Combination of disintegrants
4. Presence of surfactant
5. Hardness of tablet
6. Nature of drug substance

Table 2: Some examples of enzymes as a disintegrating agent

Enzyme	Binder
Amylase	Starch
Protease	Gelatin
Cellulose	Cellulose and its derivative

6.4 Types of superdisintegrants

- (i). Natural
- (ii). Synthetic
- (iii). Co-processed

6.4.1. Natural

These are various plant based material. Plant based material serve as an alternative to synthetic products because of following reasons;

- Local accessibility
- Eco-friendly
- Bio-acceptable
- Renewable source and low price as compared to synthetic products
- Example: Lepidus sativum , Locust bean gum, Isapgihula Husk (Plantago ovata), Hibiscus rosa sinesis linn. Mucilage etc.

6.4.2. Synthetic

Advantages of synthetic superdisintegrants:

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intragranularly

6.5 Patented technologies^[43,44]

Some of these patented technologies are as:-

6.5.1. Zydis technology

Using the concept of Gregory et al., R.P.Scherer has patented zydis technology. Zydis is a unique freeze-dried oral solid dosage form that can be swallowed without water as it dissolves instantly on tongue in less than 5 seconds. The drug is physically trapped in a water-soluble matrix, and then freeze-dried to produce a product that rapidly dissolves. The matrix consists of water-

soluble saccharides and polymer (gelatin, dextran, alginates) to provide rapid dissolution and to allow sufficient physical strength to withstand handling. Water is used during the process to produce porous units for rapid disintegration. Various gums are used to eliminate the sedimentation problem of dispersed drugs. Glycine is used to prevent the shrinkage of zydis unit during the process and in long-term storage. As the zydis dosage form is weak in physical strength, unit is contained in peelable blister pack, which allows removal of product without damaging it.

6.5.2. Orasolv technology

CIMA labs have developed Orasolv technology. The system essentially makes tablets that contain taste masked active ingredients and effervescent disintegrating agent which on contact with saliva, rapidly disintegrates and releases the taste mask active ingredient. The tablets made by direct compression at very low compression force in order to minimize oral dissolution time. The tablets so produced are soft and friable and are packaged specially designed pick and place system. The taste masking associated with Orasolv formulation is two folds. The unpleasant flavour of a drug is not merely counteracted by sweeteners or flavours; coating the drug powder and effervescence are means of taste masking in Orasolv.

6.5.3. Durasolv technology

Durasolv is CIMA's second generation fast dissolving tablet formulation. Produced in a similar fashion to that of orasolv, durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction produced during tableting. The durasolv product is thus produced in a faster and more cost effective manner. One disadvantage of durasolv is that the technology is not compatible with larger doses of active ingredients, because formulation is subjected to high pressures on compaction. Durasolv is currently available in two products nulev and zorlip.

6.5.4. WOWTAB technology

WOWTAB technology is patented by Yamanouchi. Wow means "without water". WOWTAB is an intrabuccally soluble, compressed tablet consisting of granules made with saccharides of low and high mouldability. The combination of high and low mouldability is used to obtain a tablet of adequate hardness and fast dissolution rate. Mouldability is the capacity of the compound to be compressed. Low mouldability means the compounds show reduced compressibility for tableting and rapid dissolution rate. But in case of high mouldability compounds this context is reversed. In this the active ingredient is mixed with low mouldability saccharides and granulated with high mouldability saccharides and then compressed into tablet. The wowtab formulation is stable to environment due to its significant hardness than Zydis or Orasolv. WOWTAB product is suitable both for conventional bottle and blister packaging.

6.5.6. Flash dose technology (Fuisz Technologies, Ltd.)

Fuisz has patented the FlashDose technology. The FlashDose technology utilizes a unique spinning mechanism to produce floss like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. FlashDose tablet consists of self-binding sheaf form matrix termed "floss". The procedure has been patented by Fuisz and known as "Shearform". Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of floss-like material, small spheres of saccharide can be produced to carry the drug. The procedure of making microspheres has been patented by Fuisz and known as "Ceform".

6.5.6.1. Shearform technology TM

The technology is based on the preparation of floss that is also known as 'Shearform Matrix', which is produced by subjecting a feed stock 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 floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide aciform flow properties and this facilitate blending the recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet.

6.5.6.2. Ceform technology TM

In ceform technology microspheres containing active 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 the ceform machine throws the dry drug blend at high speed through small heated openings. 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.

6.5.7. Flashtab technology

This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like microencapsulation, coacervation and extrusion-spheronization. The microcrystals or microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets.

6.5.8. Oraquick technology

The oraquick fast dissolving tablet formulation utilizes a patented taste masking technology by K. V. Pharmaceutical Company, who claim that its taste masking technology i.e. microsphere technology (micromask) has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind and therefore leads to faster and more efficient production. Tablet with significant mechanical strength without disrupting taste masking are obtained after compression.

6.5.9. Fastwrap system

BioProgress had developed novel tablet cores with a high disintegration profile that were easily coated using the TabWrap finishing process. The FastWrap system combines the TabWrap process with the company's patented novel tablet core technology to create coated tablets that can rapidly disintegrate and dissolve, allowing for a faster onset of action. The FastWrap technology can also be used to manufacture film-flavoured orally disintegrating tablets. As standard coating techniques tend to involve spraying on a coating that has been dissolved in liquid, they have run into problems with tablets that incorporate highly moisture sensitive superdisintegrants or excipients. The TabWrap system, on the other hand, is a completely dry coating process.

6.5.10. Nano crystal technology

RDT, Elan's 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 in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities

of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible.

6.6. Conventional techniques^[43, 44, 45]

6.6.1. Direct compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. FDTs can be prepared by using this technique because of the good availability of improved excipients especially super-disintegrants and sugar based excipients.

6.6.2. Freeze drying or lyophilization

It is one of the first generation techniques for preparing FDTs, in which sublimation of water takes place from the product after freezing. The formulations show enhanced dissolution characteristics due to the appearance of glossy amorphous structure to bulking agents and sometimes to drug. The advantage of using freeze-drying process is that pharmaceutical substances can be processed at non elevated temperature, thereby eliminating adverse thermal effects. High cost of equipment and processing limits the use of this process. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms.

6.6.3. Tablet molding

There are two types of molding process 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 molded plates to form a wetted mass (compression molding). Below Air-drying is done to remove the solvent. The tablets manufactured so formed are less compact than compressed tablets and possess a porous structure that hastens dissolution. In the heat molding process a suspension is prepared that contains a drug, agar and sugar (e.g. mannitol or lactose). This suspension is poured in the blister packaging wells, and then agar is solidified at the room temperature to form a jelly and dried at 30°C under vacuum. The main concern about these molded tablets is their mechanical strength, which can be achieved by using binding agents.

6.6.4. Cotton candy process

A matrix known as 'floss', with a combination of excipients, either alone or with drugs is prepared by using shear form technology. The floss is a fibrous material, similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266°F. However, other polysaccharides such as polymaltodextrins and poly-dextrose can be transformed into fibers at 30–40% lower temperature than sucrose. Due to this

modification thermolabile drugs can be safely incorporated into the formulation⁴⁵. This process results in a highly porous product and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps are:

- Floss blend
- Floss processing
- Floss chopping and conditioning
- Blending and compression

6.6.5. Sprays-drying

Spray-Drying is used for the preparation of FDTs. The formulations contained hydrolyzed and non hydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose as a disintegrant. By adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate) disintegration and dissolution were further enhanced. The porous powder was obtained by spray drying the above suspension which was compressed into tablets. Tablets manufactured by this method shows disintegration time < 20 sec in an aqueous medium^[46].

6.6.6. Sublimation

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Mouth dissolving tablets with highly porous structure and good mechanical strength have been developed by this method.

6.6.7. Mass - extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. This softened mass is extruded through the extruder or syringe and a cylindrical shaped extrude is obtained which are finally cut into even segments using heated blade to form tablets. Granules of bitter drugs can be coated using this method to mask their taste.

6.6.8. Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by wet-milling technique. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into MDTs.

6.6.9. Phase transition process

FDT were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol^[47].

6.6.10. Three-dimensional printing (3DP)

The 3DP method provides zero order drug delivery, patterned diffusion radiant drug release by micro structure diffusion barrier technique, cyclic drug release and another drug release profiles. The technique is often referred to as solid free form fabrication or computer automated manufacturing or layered manufacturing²⁶. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the

drug acetaminophen were prepared automatically by 3DP system²⁷. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume.

6.6.11. Fast dissolving films

In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.) drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film³⁰. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2 x 2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste. It has been shown in Table 3.

Table 3: A comparison of conventional solid dosage forms and mouth dissolving tablets

Conventional solid dosage forms	MDTs
Swallowing problem interferes with patient compliance	Disintegrates in oral cavity, improving patient compliance
Reaches stomach in solid form, where it disintegrates and is absorbed	Reaches stomach in liquid form, which has several advantages: <ul style="list-style-type: none"> • Improved patient compliance • Faster onset of remedial action • Patient convenience

6.7. Evaluation of mouth dissolving tablet^[49, 50]

MDTs formulations have to be evaluated for the following evaluation test.

6.7.1. Size and shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

6.7.2. Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer

6.7.3. Uniformity of weight

As per I.P. procedure for uniformity of weight was followed, 20 tablets were taken and their weight was determined individually

and collectively on a digital Weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

6.7.4. Tablet hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

6.7.5. Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A pre weighed tablet was placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test

tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentages:

$$\% \text{ Friability} = \frac{\text{loss in weight}}{\text{Initial weight}} \times 100$$

6.7.6. *In-vitro* disintegration test

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

6.7.7. *In-vivo* disintegration test

The test was carried out on 2 or 3 tablets using in the mouth and the time in second taken for complete disintegration of the tablet was measured in few seconds.

6.7.8. Wetting time

The method reported by Yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

7. 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.

8. References

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