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FAST DISSOLVING DRUG DELIVERY SYSTEM: AN OVERVIEW ON NOVEL DRUG DELIVERY SYSTEM

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1. INTRODUCTION

A quick dissolving drug conveyance framework, by and large, is a tablet which deteriorates or breaks down in the buccal depression without the need for water or biting.Most fast dissolving delivery system films must contain substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed via the patient's saliva along with the soluble and insoluble excipients. Enhanced patient compliance is a main benefit of the fast-dissolving drug delivery systems. Other benefits of fast-dissolving tablet systems include easy of swallowing, no water needed for administration, and accuracy of dosage. These additional, superior benefits allow patients to take their medication anytime and anyplace under all conditions. These tablets are any very porous or integrally soft-molded matrices or tablets compacted at very low compression forces in order to maximize tablet porosity and minimize oral dissolution or disintegration time. Quick-Dis™ however, comprises a tough, solid, soft, flexible film and does not need special packaging. It is thin and can be approved in a patient's pocket, wallet.[1]

1.1 Overview of oral cavity

Buccal cavity is that area of mouth defined by the lips, cheeks, hard palate, soft palate and floor of mouth. It is consists of two regions.

- Outer buccal vestibule, which is bounded via cheeks, lips, teeth and gingival (gums).
- Buccal cavity proper, that extends from teeth and gums back to the fauces (which lead to pharynx) with the roof with the hard and soft palate. The tongue projects from the surface of the cavity.[2]

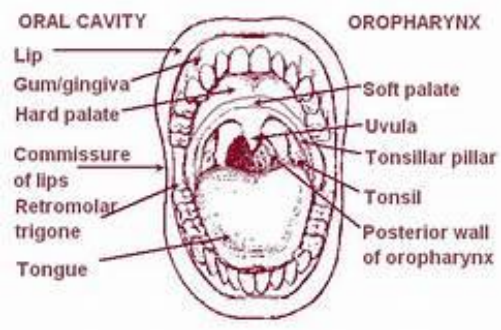

Figure 1.1: Structure of Oral cavity.

The drug administered via the buccal mucosa achievement access to the systemic circulation done a network of arteries and capillaries. The main artery supplying the blood to the buccal cavity is the external carotid artery. The intravenous backflow goes over branches of capillaries and veins and finally taken up by the jugular vein.

Sublingual glands

Salivary glands are current in the surface of the mouth underneath the tongue. They are also identified as sublingual glands. They are produce mucin in turn produces saliva. The fluid which is produced in the glands becomes mix by the food, so the food gets easily chewed. The absorption is transmission of the drug from its site of administration into systemic circulation, therefore it can be said that absorption is directly proportional layer thickness. The absorption of the drug follows in this way Sublingual >Buccal > Gums>Palatal. Due to high permeability and rich blood supply, the sublingual route can yield fast onset ofaction thus the drug with short delivery period can be carried and dose regimen is normal.

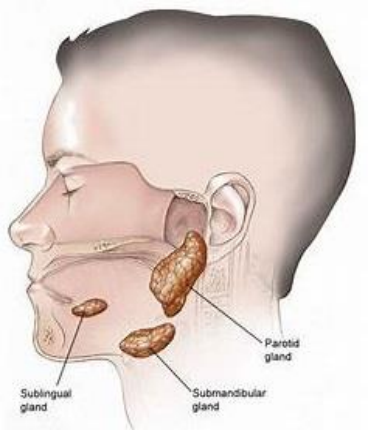

Fig.1.2: Diagram of the sublingual gland[3]

1.2. FAST DISSOLVING DRUG DELIVERY

Overview of Fast Dissolving Dosage Form

For the last two periods, there has been an improved request for more patient compliant dosage forms. As a result, there are now about 350 drug delivery corporations a medical device companies. The request for their technologies was about $14–20 billion in 1995 and, conferring to industry reports; this is expected to grow to $60 billion annually.[4,5] Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most importantly, patient compliance. Drug deposition and coating by Electrostaticmethod[6], and computer-assisted three-dimensional printing (3DP) tablet manufacture have also newly become available.[7]

Fast dissolving drug-delivery systems were first established in the late 1970s as another to tablets, capsules, and syrups for pediatric and geriatric patients who practice problems swallowing traditional oral solid-dosage forms. Oral fast-dispersing dosage forms that novel technologies are also known as fast dissolve fast dissolve, quick melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. By definition "a solid dosage form that dissolves or disintegrates rapidly in the oral cavity, resulting in solution or suspension without the essential for the administration of water is known as an oral fast-dispersing dosage form". Difficulty in swallowing (dysphagia) is joint among all age groups, mainly in elderly, and is also seen in swallowing conventional tablets and capsules.[8] an projected 35% of the general population, and an further 30–40% of elderly established patients and 18–22% of all persons in long-term maintenance facilities, smart from dysphagia. The most common complaint was tablet size, surface, form and taste. The problem of swallowing tablets was more apparent in geriatric and pediatric patients, as well as travelling patients who may not have complete access to water.[10]

Current Oral Fast Dissolving Dosage Form Technologies

Although several technologies are available, few have reached profitable marketed products. Table 1.1 shows the classification of these technologies according to core manufacturing processes.

Table 1.1 Current Oral Fast Dissolving tablet technologies

Technologies	Company
I. Conventional tablet processes with modifications	
WOWTAB®	Yamanouchi Pharma, Technologies, 1050 Arastradero Road Palo Alto, CA, USA.
ORASOLV®	Cima Labs, Inc, 10000 valley Hill Road, Eden Prairies MN, USA.
EFVDAS®	Elancorp, MonkslandAthlone County Westmeath Ireland.
FLASHTAB®	Prographarm, chaueauneuf-En-Thymeraia, France.
II. Freeze drying method	
ZYDAS®	R.P. Scherer, Frankland Road, Swindon, UK
LTOC®	Farmalyoc, 5AV Charles Marting, Maisons-Alfort, France.
QUICKSOLV®	Janseen Pharmaceuticals, 1125 Trenton-Harbourton Road, Titusville NJ, USA.
III. Floss formation	
FLASHDOSE®	Fuisz Technologies, 14555 Avion At Lakeside, Chantilly VA, USA.

Classification of Fast Dissolving Technology

For easy of description, it can be divided in to three broad groups.

a) Lyophilized systems,
b) Compressed tablet-based systems,
c) Thin film strips/Fast dissolving films (FDFs)

a) The lyophilized systems

In thisfuture the most successful among them in terms of sales value, sales volume and number of worldwide product approval. These systems containa suspension or solution of drug which equipment around with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The ensuing units have a very high porosity, which allows fast water or saliva penetration and very rapid disintegration. This system depending on whether the active ingredients are soluble or insoluble drugs for dose-handling capability with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more fast disintegration than tablet-based systems.

b) Compressed tablet-based systems

This system is using standard tablet technology by direct compression of excipients. Depending on manufacture method, the tablet tools have different levels of hardness and friability. These results in variable disintegration presentation and packaging wants, which can range from standard HDPE bottles or blisters complete to more specialist pack designs for product protection, e.g. CIMA Labs'- PackSolv. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is accomplished through formulating using water soluble

excipients, or Superdisintegrants or effervescent components, to allow fast penetration of water into the core of the tablet. The one exclusion to this method for tablets is Biovail's Fuisz technology. It uses the proprietary Shear form system to produce drug-loaded candy floss, which is then used designed for tableting with other excipients. Theoretically accommodate relatively high doses of drug material; including taste masked coated particles in this system. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage systems.[11]

c) Oral Thin Films (OTF/FDF)

Fast-dissolving thin polymer films for fast buccal delivery are becoming an increasingly popular formulation option as of their wide and varied benefits.[12]

1.3.FAST DISSOLVING TABLETS

Patient compliance is one of the most significant facets in the pharmacy practice. Now days, pharmacy companies are coming up without advance of new drug delivery systems to confirm the delivery of the drugs to the patients efficiently and with fewer side effects. Solid dosage forms are popular since of self-medication, easy of administration, accurate dosage, pain avoidance and greatest importantly the patient compliance. The buccal route of administration is measured as the most widely accepted route because of its convenience of self-medication, compaction, and ease of manufacturing, ease of administration, accurate dose, safest and economical route. Established a novel oral dosage forms known as Fast disintegrating tablets (FDTs orally disintegrating tablets (ODTs) or mouth melting tablets(MMTs) or mouth dissolving tablets(MDTs) which disintegrate quickly in saliva, usually in a matter of seconds, without the essential to take water. Recent market studies show that more than half of the patient population prefers FDTs to other dosage forms. Mouth dissolving tablets are formulated mostly by two techniques first use of superdisintegrates like crosscarmellose sodium, sodium starch glycolate and crosspovidone.

Drug delivery systems (DDS) are a planned tool for expanding markets, extending product life cycles and producing opportunities. Oral administration of drug is the most general route for systemic effects due to its easiness of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Injections generally are not favored for use by patients unless facilitated through urbane auto injectors. Inhalation is one good other system to deliver these drugs, but the increased research into biopharmaceuticals so far has produce mainly chemical entities with low molecular weights.[13]

1.3.1. Advantages of FDTS

- The FDTs do not requirement water for swallowing unlike conventional dosage forms.
- This is very convenient for patients who are travelling or do not have immediate access to water, and thus, offer improved patient compliance.
- Bioavailability of drugs is greater due to absorption from mouth, pharynx, and esophagus.
- Pregastric absorption can result in enhanced bioavailability and because of reduced dosage, improved clinical performance complete a reduction of unwanted effects.
- Therapeutic fast onset action as tablet is disintegrated rapidly along with quick dissolution and absorption in buccal cavity.
- Take the tablet when show good mouth feels, especially for pediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.
- Minimum risk of suffocation in airways due to physical obstruction, when ODTs are swallowed, thus they provide improved safety and compliance with their administrations.
- Rapid drug therapy intervention is potential.
- Conventional processing and packaging equipment permit the manufacturing of tablets at low cost.
- Not specific packaging is required. It can be packaged in push through blisters.
- Afford new business opportunities in the form of product differentiation, patent-life extension, uniqueness, line extension, and life- cycle management, and exclusivity of product advertising.

Some advantages of the current oral fast dissolving drug delivery system are shown in the figure-1 given below.[13,14]

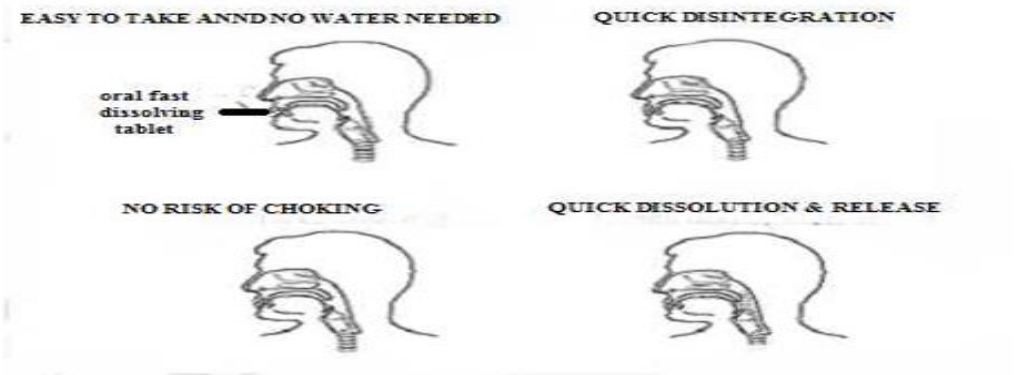

Figure 1.3: Advantages of Oral Fast Dissolving Tablet.

1.3.2. Disadvantage

- Disadvantage of most ODT is that they are fragile and brittle.
- Drugs with relatively largely doses difficult to formulate into FDT e.g. antibiotic.
- It need special package for protection during storage and transportation.

1.3.3. Limitations of FDTS

- Patients who concurrently take anti-cholinergic medications may not be the best candidates for FDTs.
- Tablets usually have insufficient mechanical strength. Later, it needs careful packaging and handling.
- Tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- They are more susceptible to degradation by humidity and temperature.
- Its is hygroscopic in nature hence must be keep in dry place.
- Some time it possesses mouth feeling.
- MDT requires special packaging for properly stabilization & safety of stable product.
- Drugs difficult to formulate into FDT with relatively larger doses.
- Drugs is short half-life and frequent dosing and those whom need controlled or sustained release are unsuitable candidates of FDTs.
- Drugs with relatively large doses are difficult to formulate into FDTs.[13]

1.3.4. Ideal properties of FDTS

- Not require water or other liquid to swallow
- Easily dissolve or disintegrate in saliva within a few seconds.
- Have a pleasing taste.
- Leave negligible or no residue in the mouth when administered.
- Be portable and easy to transport.
- Be able to be manufactured in a simple conventional manner within low cost.
- Be less sensitive to environmental conditions like temperature, humidity etc.[14]

1.3.5. Challenges for development of FDTS

Mechanical strength and disintegration time

It is evident that increasing the mechanical strength will stay the disintegration time. Therefore a good compromise amongst these two parameters is always essential. FDTs are formulated to obtain disintegration time generally less than a minute. While doing so, keeping a good mechanical strength is a major challenge.

Taste masking:

As greatest drugs are unpalatable, fast disintegrating drug delivery systems typically contain the medicament now a taste- masked form. Delivery systems disintegrate or dissolve in patient's buccal cavity, therefore releasing the active ingredients which come in contact concluded the taste buds; therefore, taste-masking of the drugs becomes serious to patient compliance.

Aqueous solubility

Water-soluble drugs position several formulate ion challenges for they form eutectic mixtures, which result in freezing-point depression and the format ion of a glossy solid that may collapse upon drying because of loss of supportive structure during the sublimate ion process.

Hygroscopicity

Hygroscopicity is, of passage, a main characteristic of a powder. It can be shown, roughly, designed for a fairly soluble compound that the Hygroscopicity is related to its solubility. FDTs should have low sensitivity to moisture. This problem can be especially challenging because many highly watersoluble excipients are used in formulation to improve fast-dissolving properties as well as to generate good mouth feel.

Amount of drug

The application of technologies used for FDTs is incomplete by the amount of drug that can be incorporated into every unit dose. Aimed at lyophilized dosage forms, the drug dose needlower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs.

Size of tablet

It takes labeled thattablet to swallow is 7-8 mm the easiest size while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Mouth feel

FDTs should not disintegrate keen on larger particles in the oral cavity. The small particles generated after disintegration of the FDTs. Moreover adding of flavors and cooling agents like menthol improve the mouth feel.

Sensitivity to environmental conditions

FDTs should demonstration low sensitivity to environment circumstances such as moisture and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water.

Cost

The technology used for FDTs should be acceptable in terms of cost of the final product. Zydis and Orasolv that require different technologies and specific packaging increase the cost to a remarkable extent.

Tablet strength, Friability and porosity

In directive to allow fast disintegrating tablets to disintegrate in the mouth, they are made of both very porous or soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to

handle, often requiring specialized peel-off blister packaging.[13]

1.3.6. Drug selection criteria

The drug selection criteria for fast dissolving tablets are below,

- Partially non- ionized at the oral cavities Ph.
- Ability to permeate the buccal mucosa.
- Small to moderate molecular weight are used.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Good stability in water and saliva.
- Drugs which have lower bioavailability are good candidates for FDT.
- Short half-life and frequent dosing drugs are unsuitable for FDT.
- Very bitter taste and odor drugs are inappropriate for ODT. Patients who concurrently take ant cholinergic medications may not be the greatest candidates for these drugs.
- Drugs having ability to wordy and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are careful model for FDT formulations.
- Drugs which require controlled or sustained release are unfitting candidates of fast dissolving oral dosage forms.

1.3.7. Criteria for excipients

The ideal characteristics of excipients for buccal fast dissolving tablets include.

- It must be able to disintegrate rapidly.
- Their individual properties should not affect the ODTs.
- It should not have any interaction by drug and other excipients.
- It should not delay in the efficacy and organoleptic properties of the product.
- The final integrity and stability of the product of selecting binder (a single or combination of binders) care must be taken.
- The melting point of the excipients used should be in the range of 30-35ºC.
- The binder may be in liquid, semi-solid, solid or polymeric in nature.[13]

1.3.8. Various approaches for FDTS

Attributablethe fast-dissolving property of the tablet is quick entrance of water into the tablet matrix ensuing in its quick disintegration. Later, contain maximizing the porous structure of the tablet matrix, including the appropriate disintegrating agent, and by highly water soluble excipients in the formulation the basic methods to developing fast dissolving tablets.

1.3.9. Need for development of FDTS

The need for development of FDTS contains following factors.

Patient factors

Fast disintegrating dosage forms are mainly suitable for patients, who aimed at one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These comprise the following.

- Patients who are unwilling to take solid preparation due to fear of unpleasant.
- An eight-year old with allergies who needs a more convenient dosage form than antihistamine syrup.
- Pediatric and geriatric patients who have problem in swallowing or chewing solid dosage forms.
- A middle-aged woman undergoing radiation therapy aimed at breast cancer may be too nauseous to swallow her H2- blocker.
- A patient with persistent nausea, who may be journey, or has little or no access water
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to evade their daily dose of an atypical antipsychotic.
- Very elderly patients who may not be clever to swallow a daily dose of antidepressant.

Effectiveness factor

Better bioavailability and quicker onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity sources Pregastric absorption from some formulations in those cases where drug dissolves quickly. Buckle, pharyngeal and gastric areas 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 considerable portion of absorption in the buccal cavity andPregastric segments of GIT.

Manufacturing and marketing factors

As a drug approaches the end of its patent life, it is shared for pharmaceutical manufacturers to grow a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to spread market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while contribution its patient population a more convenient dosage form. This leads to increased income, while also targeting underserved and undertreated patient people. Marketers build a better brand and company image when they proposal a unique easier-to-take form that contents the need of an underserved.[15}

1.3.10. Formulation aspects in developing FDTS

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the FDTs formed vary in various properties such as.

1. Mechanical strength of tablets
2. Taste and mouth feel

3. Swallow ability
4. Drug dissolution in saliva
5. Bioavailability
6. Stability

1.3.11. Excipients used in fast dissolving tablets

Excipients balance the properties of the actives in rapid melting tablets. This loads a thorough understanding of the chemistry of these excipients to stop interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is significant in the formulation of fastdissolving tablets. These inactive food-grade ingredients, once combined in the formulation, impart the desired organoleptic properties and product efficacy.

Superdisintegrants

Disintegrates are substances regularly comprised in tablet formulations and in some hard shell capsule formulations to promote humidity penetration and dispersion of the matrix of dosage form in dissolution fluids. Superdisintegrants are generally used at a low concentration, typically 1-10% by weight relative to total weight of dosage unit. Commonly employed Superdisintegrants are crosscarmellose sodium (Ac-Di-Sol), Crosspovidone (CP), sodium starch glycolate (SSG) etc. which represent example of cross-linked cellulose, crosslinked polymer and cross-linkedstarch individually. Selection of appropriate formulation excipients and manufacturing technology is necessary for obtaining the optimized design features of orally disintegrating dosage forms.

Selection of Superdisintegrants

Though Superdisintegrants chiefly affect the rate of disintegration, but when used at high levels they can also touch mouth feel, tablet hardness and friability. Therefore, various ideal factors to be measured while selecting an appropriate Superdisintegrants for a particular formulation should.

- Yield fast disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.
- Be compactable sufficient to produce less friable tablets.
- Produce good mouth feel to the patients. Therefore, small particle size is preferred to achieve patient compliance.
- Have good flow; meanwhile it improves the flow characteristics of total blend.

Bulking materials

Gives functions of a diluents, filler and cost reducer. Bulking agents advance the textural characteristics that in turn improve the disintegration in the mouth, besides adding bulk also decreases the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolysate for higher aqueous solubility and good sensory perception.

- Mannitol in particular has high aqueous solubility and good sensory perception.
- Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.
- The excipients could be ordered in descending order in terms of their brittleness: microcrystalline cellulose > spray-dried lactose > beta lactose > alpha lactose > alpha lactose monohydrate >dicalciumphosphatedihydrate.
- The sugar based excipients which are usually used are especially bulking agents (like dextrose, fructose, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and later impart taste masking property and provide pleasing mouth feel.

Lubricants

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth sad into the stomach.

Flavors and Sweeteners

Flavors and taste-masking agents type the products more palatable and pleasing for patients. The addition of these ingredients contributions in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavors can be used to recover the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners counting sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners funds a pleasant taste as well as bulk to the composition.

1.3.12. Mechanisms of tablet disintegration

- By capillary action (Wicking)
- By swelling
- Because of heat of wetting
- Due to release of gases
- By enzymatic action
- Due to disintegrating particle/particle repulsive forces
- Due to deformation.

By capillary action (Wicking)

Disintegration by capillary action is continuously 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 fails the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet hinge on upon hydrophilicity of the drug/excipient and on tabletting conditions. For these types of disintegrates, 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.

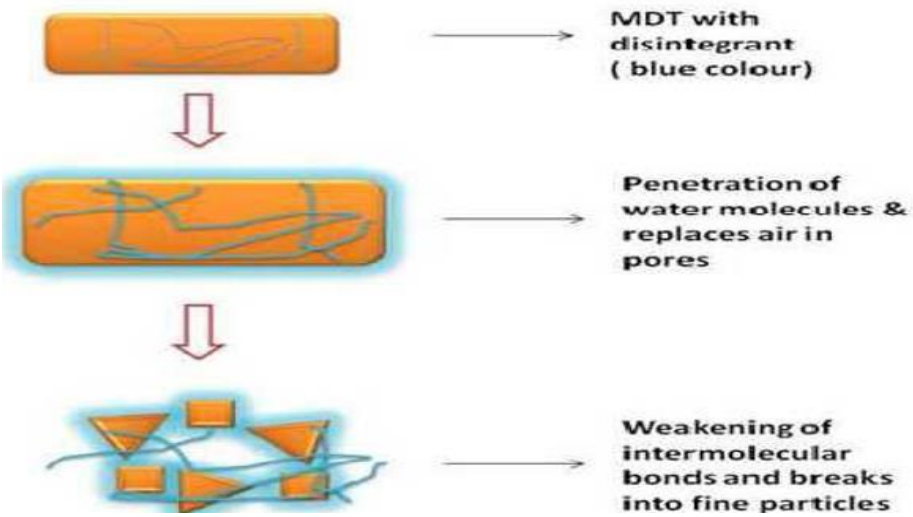

Figure 1.4: Wicking Mechanism of FDTS.

By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling tablet 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 slow down.

Because of heat of wetting (air expansion)

When disintegrates with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet.

Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrates are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

By enzymatic reaction

Here, enzymes present in the body act as disintegrates. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radialdirection, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with non swellabledisintegrates. 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.

Due to deformation

Hess had proved that 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.[15,16]

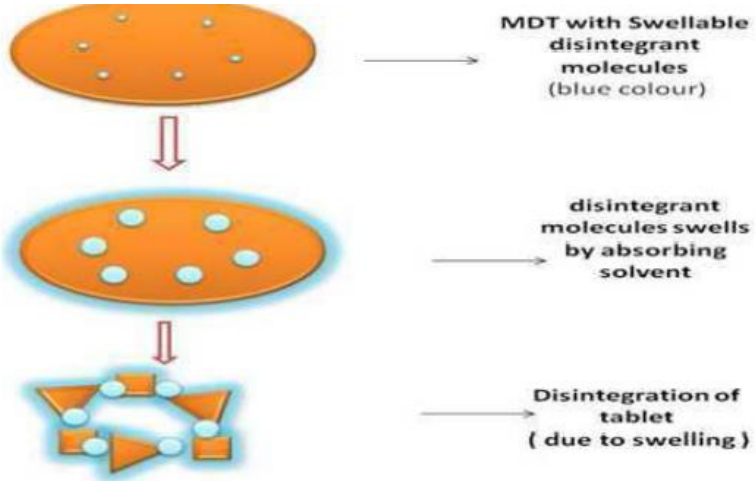

Figure 1.5: Swelling mechanism of FDTS.

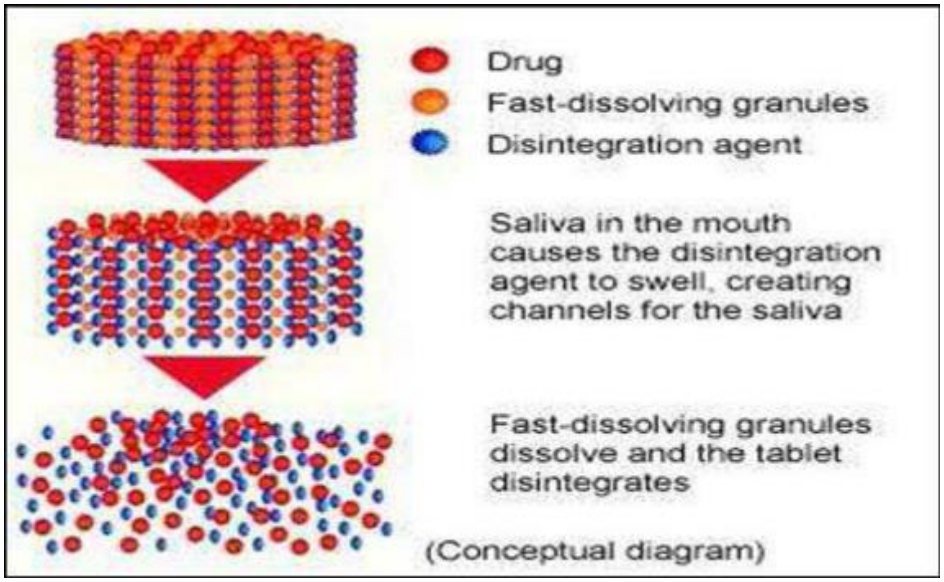

Figure 1.6: Conceptual mechanism of FDT Disintegration (By release of gases).

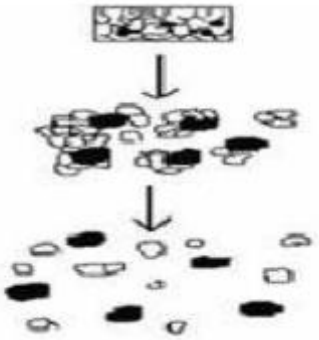

Figure 1.7: Disintegration of FDTS by Deformation.

Table no. 1.2 list of superdisintegrats.

Superdisintegrants	Example	Mechanism action	Special comment
Crosscarmellose® Ac-di-sol® Nymce ZSX® Primellose®Solutab® Vivasol® L-HPC	Crosslinked Cellulose	-swells 4-8 folds in <10 second. -swelling and –wicking both.	Swells in two dimension . -direct composition or granulation. -starch free.
Crosspovidone® CrosspovidoneM® Kollidon® polyplasdone®	Crosslinked PVP	-swells very little and retutrns to original size after compression but act by capilliary action.	Water insoluble and spongy in nature so get porous tablet.
Sodium starch glycolate Explotab® Primolgel®	Crosslinked Starch	-swells 7-17 fold in <30 second	Swells in three dimensions an high level serve as sustain Release matrix
Alginic acid NF Satialgine®	Crosslinked Alginnic acid	-rapid swelling in aqueous medium or wicking action .	Promote disintegration in both dry wet granulation
Soy polysaccharides Emcosoy®	Natural super Disintegrate		-does not contain any starch or sugar .used in nutritional product.
Calcium silicate		-wicking action	Highly porous, optimum concentration is between 20-40%.

1.3.13. Techniques for Preparing Fast dissolving Tablets

Many techniques have been reported for the formulation of Fast dissolving tablets orOrodispersible tablets.

1. Freeze drying / lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion

1. Freeze-Drying or Lyophilization

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 aluminum 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. The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

2. Tablet Molding

Molding process is of two type 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). 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 molding 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 molded 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 lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

3. Spray Drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or Crosspovidone 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 Superdisintegrants like sodium starch glycolate&crosscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4. Sublimation

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.

5. Direct Compression

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 availabilityof improved excipients especially Superdisintegrants and sugar based excipients.

(a) Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition ofSuperdisintegrants 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.

(b) Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based in Excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose,mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueoussolubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.Mizumito et al have classified sugar-based excipients into two types on the basis of molding anddissolutionrate.Type 1 saccharides (lactose and mannitol) exhibit low mould ability but high dissolution rate.Type 2 saccharides (maltose and maltilol) exhibit high mould ability and low dissolution rate.

6. Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water-solublepolyethylene glycol and methanol and subsequent expulsion of softened mass through theextruder 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.

7. Cotton candy process

This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. This technique involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have better flow properties and compressibility. This matrix is milled and blended with active ingredients as well as excipients and subsequently compressed to FDTs.

8. Phase transition

A novel method to prepare FDTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, FDTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point.[17,18]

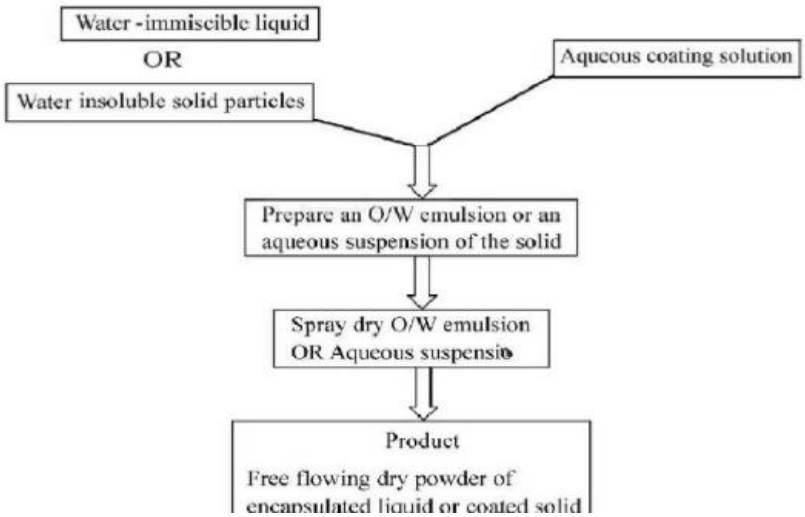

Figure 1.8: Flowchart for coating liquid and solid particles using spray-dry process.

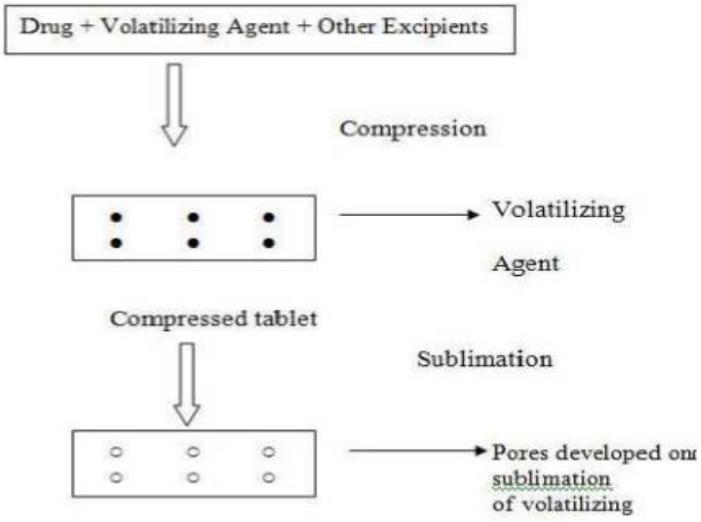

Figure 1.9: Schematic Diagram of Sublimation Technique for Preparation of FDTs.

1.3.14. Important Patented Technologies for Fast Dissolving Tablets

1. Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped ordissolved within the matrix of fast dissolving carrier material. When zydis units are put into themouth, the freeze-dried structure disintegrates instantaneously and does not require water to aidswallowing. The zydis matrix is composed of many material designed to achieve a number ofobjectives. To impart strength and resilience during handling, polymers such as gelatin, dextranor alginates are incorporated.

2. Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consistof drug, filler and a lubricant. Tablets are prepared by using conventional tablettingequipmentand have good rigidity.These can be packaged into conventional packaging system like blisters. Durasolv is inappropriate technology for product requiring low amounts of active ingredients.

3. Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is tastemasked. It also contains effervescent disintegrating agent. Tablets are made by directcompression 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 producedare soft and friable.

4. Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofenmeltlet, a new form of ibuprofen asmelt in mouth tablets prepared using flash dose technology is the first commercial productlaunched by biovail corporation. Flash dose tablets consist of self-binding shear form matrixtermed as “floss”. Shear form matrices are prepared by flash heat processing.

5. Wow tab Technology

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldabilitysaccharide is used to obtain a rapidly melting strong tablet. The active ingredient is mixed witha low mouldability saccharide (e.g. lactose, glucose, and mannitol) and granulatedwith a highmould ability saccharide (e.g. Maltose, oligosaccharides) and compressed into table.

6. Flash tab Technology

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by thissystem consists of an active ingredient in the form of micro crystals. Drug micro granules maybe prepared by using the conventional techniques like coacervation, micro encapsulation andextrusionspheronisation. All the processing utilized conventional tableting technology.

Table -1.3: List of commercially Available Fast dissolving tablets.

Trade Name	Active Drug	Manufacturer
Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexia	Olanzapine	Elililly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Zofran ODT	Ondansetron	GlaxoWellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zeplar TM	Selegilline	Amarin Corp., London, UK
TempraQuiclets	Acetaminophen	Bristol myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
Olanexinstab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA

1.3.15. Drugs to be promising incorporate in FDTS

Analgesics and Anti-inflammatory Agents: Aloxiprin, Auranofin, Azapropazone.

Anthelmintics: Albendazole, Bephenium Hydroxynaphthoate, Cambendazole.

Anti-Arrhythmic Agents: Amiodarone, Disopyramide, Flecainide Acetate.

Anti-Epileptics: Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin.

Anti-bacterial Agents: Benethamine Penicillin, Cinoxacin, Ciprofloxacin.

Anti-coagulants: Dicoumarol, Dipyridamole, Nicoumalone, Phenindione. Anti-

Anti-Epileptics: Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin.

Anti-Fungal Agents: Amphotericin, Butoconazole Nitrate, Clotrimazole.

Anti-Gout Agents: Allopurinol, Probenecid, Sulphinpyrazone.

Anti-Malarial: Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine.

Anti-Migraine Agents: Dihydroergotamine Mesyiate, Ergotamine Tartrate.

Anti-Muscarinic Agents: Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine.

Immunosuppressants: Aminoglutethimide, Amsacrine, Azathiopine, Busulphan.

Anti Protozoal Agents: Benznidazole, Clioquinol, Decoquinate.

Anti-Thyroid Agents: Carbimazole, Propylthiouracil. Anxiolytic, Sedatives.

Hypnotics and Neuroleptics: Alprazolam, Amiobarbitone, Barbitone, Bentazeparn.

Cardiac Inotropic Agents: Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C.

Corticosteroids: Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate.

Diuretics: Acetazolarnide, Amiloride, Bendrofluazide, Bumetanide, Chlorothiazide.

Anti-Parkinsonian Agents: Bromocriptine Mesylate, Lysuride Maleate.

Gastro-Intestinal Agents: Bisacodyi, Cimetidine, Cisapride, Diphenoxylate.

Histamine H,-Receptor Antagonists: Acrivastine, Astemizole, Cinnarizine, Cyclizine.

Local Anaesthetics: Lidocaine.

Neuro -Muscular Agents: Pyridostigmine. Nitrates.

Anti-Anginal Agents: Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate,

Nutritional Agents: Beta-carotene, Vitamin A, Vitamin B 2 , Vitamin D, Vitamin E, Vitamin K.

Opoid Analgesics: Codeine, Dextropropyoxyphene, Diamorphine, Dihydrocodeine,

Oral Vaccines: Vaccines designed to prevent or reduce the symptoms of diseases of which the following is a representative Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, Aids,[19]

1.3.16. Future prospects

There are several biopharmaceutical advantages such as improved efficiency over conventional dosage forms for Fast disintegrating tablets. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. Based on conventional techniques, new techniques are developed like Zydis, Wow Tab, Flash tab technology and many more, which leads to getting a patent and new mark.

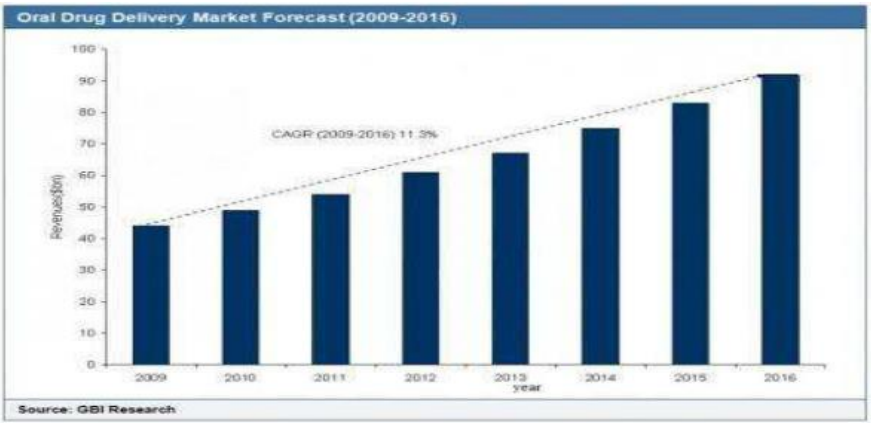

Figure 1.10: Oral Drug delivery system market forecast (2009-2016).

1.3.17. Common Reasons and Conditions for Using ODTs

Orally disintegrating tablets can be utilized for various medical conditions and patient demographics. Table no.,1.4 lists generic medical conditions that may be treated with ODTs.[20]

Table 1.4 Common Reasons and Conditions for Using ODTs.

Medication Type	Indication
Fast-acting	Pain, fever, heartburn, diarrhea, migraine, anxiety, insomnia
Compliancecritical	Parkinson's disease, Alzheimer's disease psychosis, schizophrenia, hypertension, cholesterol, transplantation
Pediatric	Cough/cold/allergy, pain, fever, ADHD

CONCLUSION

Mouth dissolving tablets are solid dosage forms containing drugs that disintegrate in the oral cavity within less than one minute the development of mouth dissolving tablets formulation is emerging and gaining popularity because it is easy to administer and leads to better patient compliance. The basic principle involved in formulating fast dissolving tablets is by maximizing the pore structure . a vacuum-drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets The main focus of this category of drug is basically on paediatric and geriatric populations and patients suffering from heart disease as these provide instant relieve from the attack as taken by the patient itself without water as it dissintigerates rapidly within the saliva which help in quick recovery and helpful to those patients founding difficulty in swallowing of tablets, as fdt has a potential advantage on conventional dosage form as the increases the bioavailability and onset of action of the drugs .the key ingredient of the formulation is the addition of a super disintigerating agent in optimum concentration which provide rapid disintigeration along with excellent mechanical strength . the product offers a promising future potential because of the availability of new technologies along with strong market acceptance and patient demand Several drug delivery technologies that can be leveraged on improving drug therapy from these dosage forms. These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds'. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach used in development of MDT is the use of superdisintegrants like Cross linked carboxymelhylcellulose (Croscarmeliose), Sodium starch glycolate (Primogel, Explotab) (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva . 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 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.

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