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Review Article

Fast dissolving tablets as a novel boon for lipophilic drugs

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ABSTRACT

The objective of this paper was to review the information about Fast dissolving tablet. Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Among them, fast dissolving drug delivery systems (FDDDS) have acquired an important position in the market by overcoming previously encountered administration problems. FDDDS 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 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 and unavailability of water. To overcome such problems, certain innovative drug delivery systems, like 'Fast Dissolving Tablets' (FDT) have been developed. FDTs dissolve in saliva within a few seconds, when put on tongue. Such FDTs 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 process, various modifications in the conventional technique, evaluation parameter, future trends for these evolving forms and patients counseling points for FDDTs.

1. INTRODUCTION

Recent advances in Novel Drug Delivery system (NDDS) aim to enhance safety and minimize toxicity of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [1].

FDDDS were first come into existence in 1970 as an alternative to tablets, syrups and capsules, for pediatric and geriatric patients [2]. Fast dissolving tablets (FDTs) are a solid single-unit dosage form that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provides a quick onset of action. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [3].

According to European pharmacopoeia, these Fast Dissolving Tablets (FDTs) should dissolve/disintegrate in less than three minutes. Fast dissolving tablets are also called as oro dispersible tablets, Mouth disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt tablets. United States

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Pharmacopoeia (USP) approved these dosage forms as ODTs. United States Food and Drug Administration (FDA) defined ODTs as "A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue" [4].

1.1 Challenges in Formulating FDTs

Challenges in formulating and manufacturing of FDTs mainly collocated as physico-mechanical properties, drug molecule and taste related properties, sensitivity to environmental conditions and cost. In order to disintegrate and swallow FDTs are made of porous or soft molded matrices make them fragile forms which requires peel-off blister packing, thus increases its cost. Drug properties have significant effect on formulation parameters like manufacturing method and thus characteristics of the final tablet. Chemical and physical properties of drugs that can exemplified as solubility, particle size, compressibility, hygroscopicity, etc. should take into consideration. Although no certain limit are defined for drug amount, generally it is advised to be around 50 w/w % or below of the entire tablet which is preferably 20 w/w % or below. The drug dose indicated that must be lower than 400 mg for insoluble drugs and 60 mg for soluble drugs where critical size to easy swallow and handle is around about 8 mm. Generally it is hard to achieve stable FDTs for environment conditions such as humidity and temperature due to most of ingredients of FDTs dissolve in minimum quantity of water. Unless the technology used for a FDT does not utilizes cost effective production method which allow to use conventional processing and packaging equipments, the cost would be increase especially in case of using patented technologies. Since most of drugs are unpalatable, proper taste masking technology is necessary to provide good taste for FDTs.

Table 1. Advantages and limitations of FDT [5, 6]

S.No.	Advantage	Limitations
1.	Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.	The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2.	Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and oesophagus.	Drugs with relatively large doses are difficult to formulate into FDTs.
3.	Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.	The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
4.	Does not require water for oral administration	Patients who concurrently take anti-cholinergic medications may not be the best candidates for FDTs.
5.	Have a pleasant mouth feel	They are more susceptible to degradation by humidity and temperature
6.	Convenient dosing	
7.	The possibility of an improved bioavailability due to rapid absorption and faster onset of action.	Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
8.	FDTs helps avoids hepatic metabolism by allowing pregastric drug absorption thus reducing the dose of drug required.	MDT requires special packaging for properly stabilization & safety of stable product
9.	FDT Allows high capacity of drug loading	Some time it possesses mouth feeling
10.	FDT passes all the advantages of solid dosage forms like good stability, easy manufacturing, unit and accurate dosing, easy handling etc.	Drugs with short half-life and frequent dosing and those whom require controlled or sustained release are unsuitable candidates of FDTs

2. MAIN INGREDIENTS USED IN PREPARATION OF FDT

Important ingredients that are used in the formulation of FDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the active ingredient and the excipients. Disintegration and solubilzation of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients and effervescent agents. Excipients balance the properties of the actives in FDDTs. This demands thorough understanding of the chemistry of these excipients to prevent interaction with the active molecules. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy.

Excipients are general and can be used for a broad range of actives, except some actives that require masking agents. Binders keep the composition of these fast-melting tablets together during the compression stage. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35°C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a

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fast- dissolving formulation for achieving the desired sensory and melting characteristics and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used. The most important ingredients of a mouth dissolving tablets are:

2.1 Super Disintegrants

Use of disintegrants is the basic approach in development of FDTs. Disintegrants play a major role in the disintegration and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant.

Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases. Sodium starch glycolate, Crosscarmellose sodium, Crospovidone, Microcrystalline cellulose, Pregelatinised starch are some of examples of disintegrants [7].

Table 2. Potential Candidate for FDT [8]

S.No.	Class	Drugs
1.	Analgesics and Anti-inflammatory Agents	Aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, enbufen, fenoprofen calcim, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamicacid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, sulindac
2.	Anthelmintics	Albendazole , bephenium hydroxy naphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate, thiabendazole
3.	Anti-Arrhythmic Agents	Amiodarone HCl, Disopyramide, flecainide acetate, quinidine sulphate
4.	Diuretics	Acetazolamideamiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene
5.	Anti-bacterial Agents	Benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin , rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim
6.	Corticosteroids	Beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisoneacetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methyl prednisolone, prednisolone, prednisone, triamcinolone.
7.	Anti-fungal Agents	Amphotericin, butoconazolenitrate, clotrimazole, econazolenitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole, undecenoic acid
8.	Anti-gout Agents	Allopurinol, probenecid, sulphinpyrazone
9.	Anti-muscarinic Agents	Atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscyamine, mepenzolate bromide, orphenadrine, oxyphencylcimineHCl, tropicamide
10.	Anxiolytic, Sedatives, Hypnotics and Neuroleptics	Alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clotiazepam, clozapine, diazepam, droperidol,ethinamate, flunanisone, flunitrazepam, fluopromazine, flupenthixol decanoate, fluphenazine decanoate, flurazepam, haloperidol
11.	Nutritional Agents	Betacarotene, vitamin A, vitamin B2, vitamin D, vitamin E, vitamin K. Opioid Analgesics: codeine, dextropropyoxyphene, diamorphine, dihydrocodeine, meptazinol, methadone, morphine, nalbuphine, pentazocine
12.	Stimulants	Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol, pemoline.

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13.	Sex Hormones	Clomiphenecitrate, danazol, ethinyloestradiol, medroxyprogesterone acetate, mestranol, methyl testosterone, norethisterone, norgestrel, oestradiol, conjugated oestrogens, progesterone, stanozolol, stiboestrol, testosterone, tibolone.
14.	Gastro-intestinal Agents	Bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mesalazine, nizatidine, omeprazole, ondansetron HCL, ranitidine HCl, sulphasalazine.
15.	Proteins, Peptides	Insulin, glucagon, growth hormone (somatotropin), polypeptides or their derivatives.

2.2 Mechanism of Action Of Disintegrants

The tablet breaks to primary particles by one or more of the mechanisms listed below:

2.2.1 By Capillary Action

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.

2.2.2 By Swelling

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

2.2.3 Because of Heat of Wetting (Air Expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents [9].

2.2.4 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 disintegrants 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.

2.2.5 By Enzymatic Reaction

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

2.2.6 Due to Disintegrating Particle-particle Repulsive Forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. As per particle repulsion theory non-swelling 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.

2.2.7. Due to Deformation

During tablet compression, disintegranted particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

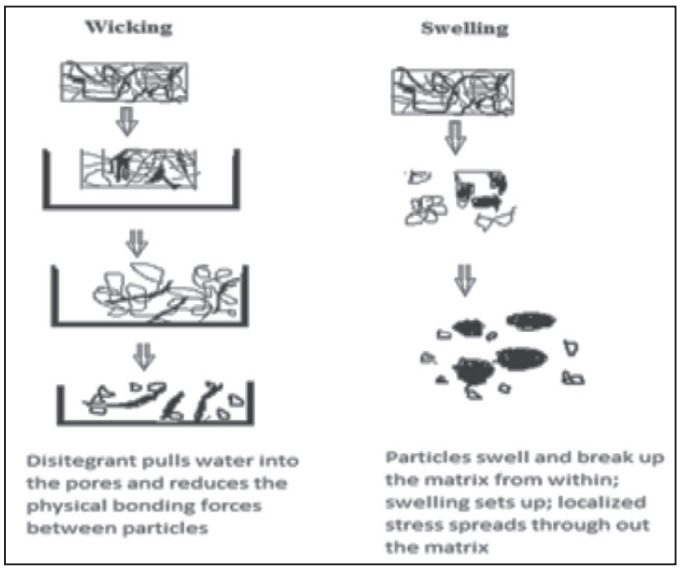

Fig. 1. Disintegration of tablet by wicking and swelling

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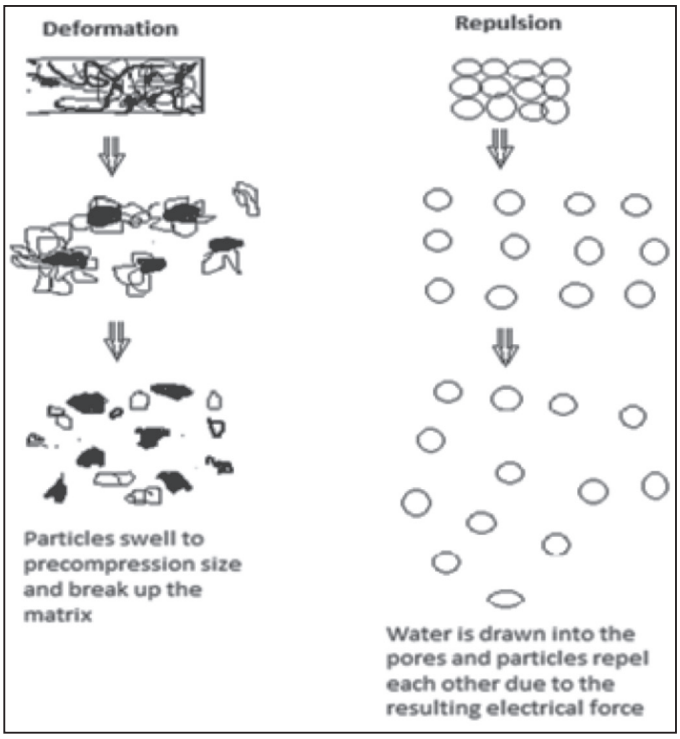

Fig. 2. Disintegration by deformation and repulsion

2.3. Sugar based Excipients

Sugar based excipients are used for taste masking and as bulking agents. Most of the dugs are having unpleasant or bitter taste and the basic requirement for designing FDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, mannitol, xylitol, dextrose and fructose are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking. But not all sugar-based materials have fast dissolution rate and good compressibility or compactability. However technologies have been developed to make use of the sugar based excipients in the design of fast dissolving tablets. Other ingredients commonly used are water soluble diluents, lubricants, antistatic agents, plasticizers, binders, colors and flavors [10].

3. CONVENTIONAL TECHNOLOGIES

3.1 Freeze Drying or Lyoplilization

Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Figures 3 and 4 show the material is frozen to bring it below its eutectic point. Then primary drying is carried out to reduce the moisture to around 4% w/w of dry product. Finally, secondary drying is done to reduce the bound moisture to the required volume. Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Freeze- dried forms offer more rapid dissolution than other available solid products. The entire freeze drying process is done at nonelevated temperature to eliminate adverse thermal effects that may affect drug stability. 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 and their limited ability to accommodate adequate concentration of drugs [11].

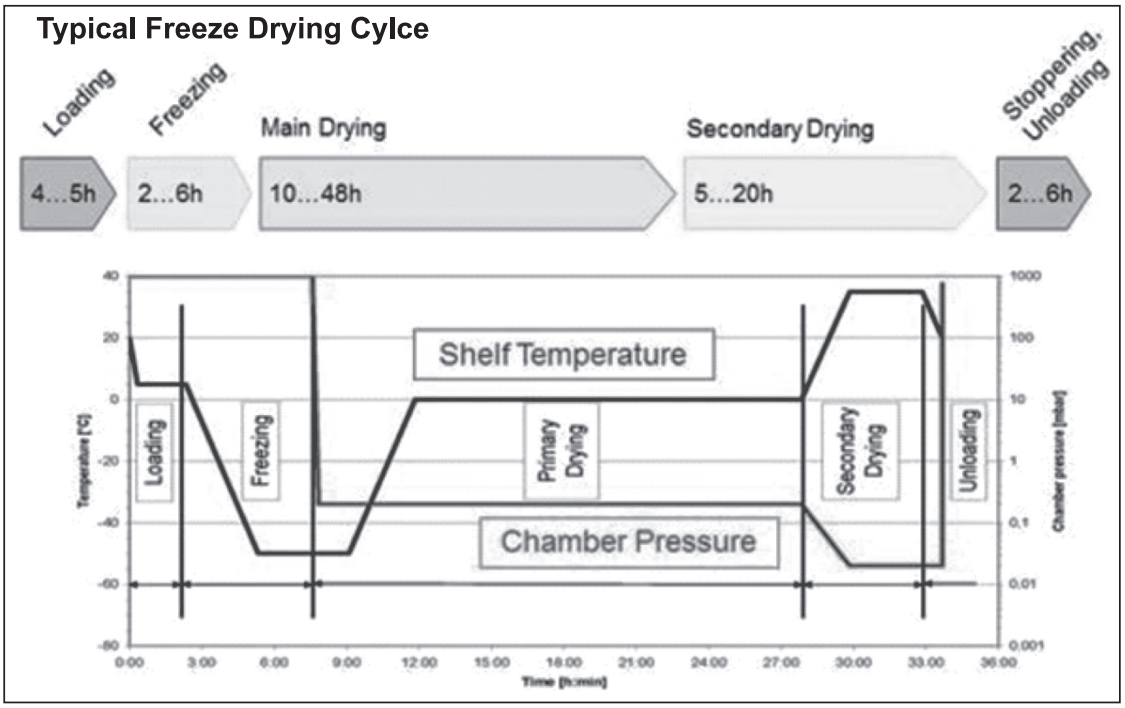

Fig. 3. Freeze drying cycle

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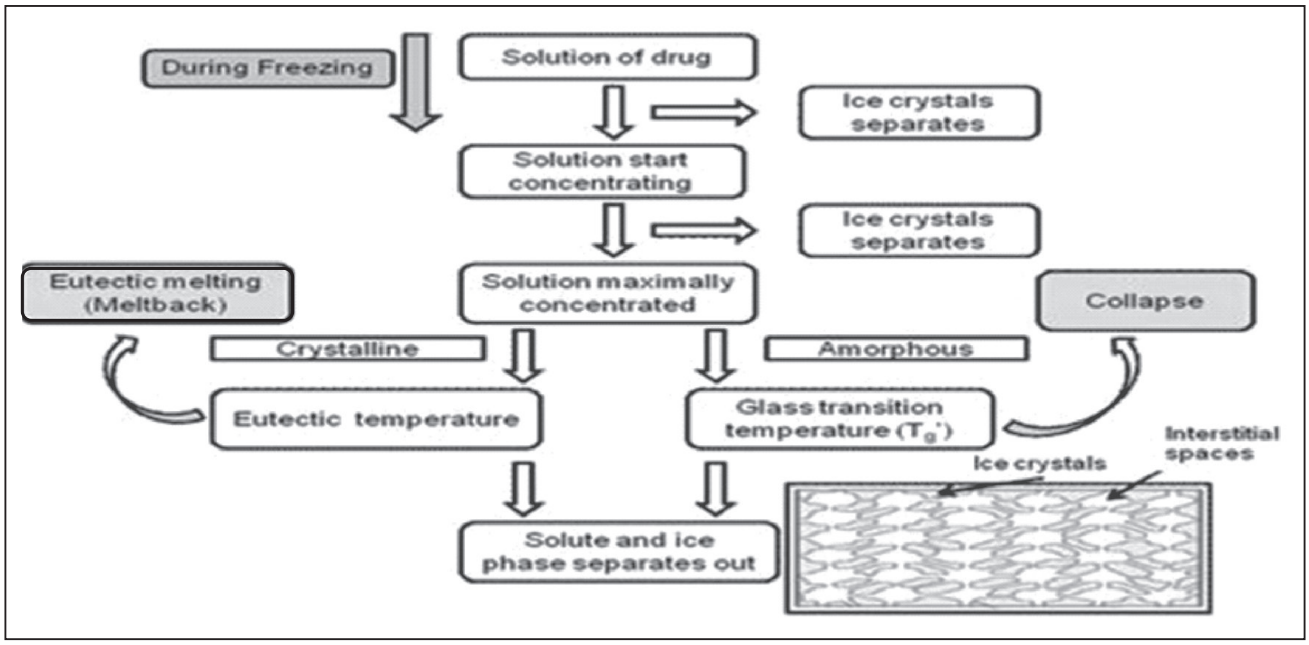

Fig. 4. Flowchart showing the concept of eutectic temperature and Tg (glass Transition) and their importance during primary drying.

3.2 Direct Compression

Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution. Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. The type of disintegrants and its proportion are of prime importance. Also factors to be considered are particle size distribution, contact angle, pore size distribution and water absorption capacity. Studies revealed that the water insoluble superdisintegrants like sodium starch glycolate and Croscarmellose sodium show better disintegration property than the slightly water soluble agents like Crospovidone, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants [12].

3.3 Molding

Molded tablets, usually prepared from soluble ingredients, by compressing a powder mixture which is moistened with a solvent, into mould plates to form a wetted mass. Recently, molded forms have been prepared directly from a molten matrix, in which the drug is dissolved or dispersed or by evaporating the solvent from a drug solution or suspension at a standard pressure.

Usually molded tablets are compressed at a lower pressure than are conventional are conventional tablets, and posses a porous structure that hastens dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Tablet produced by molding are solid dispersion. Molded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Unfortunately, moulded tablets typically do not possess great mechanical strength.

Erosion and breakage of the moulded tablets often occurs during tablet handling and when blister pockets are opened. Hardness agents can be added to the formulation, but then the rate of tablet solubility usually decreases [13].

3.4 Mass Extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with different

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super disintegrate e.g. sodium starch glycolate, croscarmellose sodium and crosspovidone etc. [10].

3.5 Melt Granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues [14].

3.6 Phase Transition Process

FDTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, 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. Heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low compactibility [15].

3.7 Sublimation

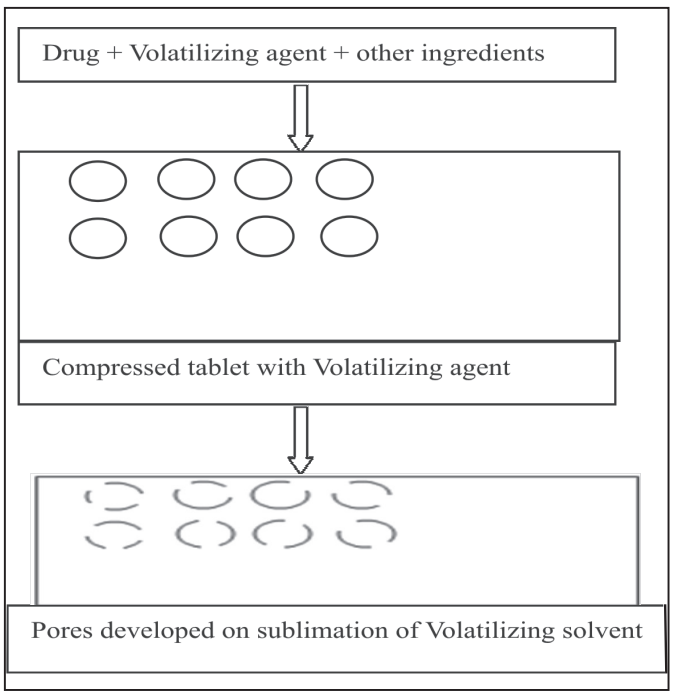

Fig. 5. Steps involved in sublimation process

The slow dissolution of the compressed tablet containing even highly water soluble ingredients is due to the fact that the low porosity of the tablets reduces water penetration into the matrix. When inert volatile solid ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane were added to along with other tablet excipients and the blend was compressed in to a tablet, which are finally subjected to a process of sublimation resulting in highly porous structures. Sublimation has been used to produce FDTs with high porosity. These compressed tablets exhibit good mechanical strength and have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva [16].

4. PATENTED TECHNOLOGIES

4.1 Zydis Technology

Zydis was the first marketed technology developed by R.P. Scherer,Inc. for formation of new generation tablets. The tablet dissolves in the mouth within seconds after placement on the tongue. Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolve in a matrix composed of two components, a saccharide e.g. mannitol and a polymer. When Zydis units are kept in the mouth the freeze dried structure disintegrates instantaneously and does not require water for swallowing. Polymers such as gelatin, dextran are incorporated to impart strength during handling. Mannitol or sorbitols are incorporated, to obtain crystallanity, elegance and hardness. Flocculating agents (e.g, xanthan gum and acacia) to provide uniform dispersion of drug particles; preservatives (e.g., parabens) to prevent microbial growth; permeation enhancers (e.g., sodium lauryl sulphate) to improve transmucosal permeability; pH adjusters (e.g, citric acid) to optimize chemical stability; flavours and sweetners to improve patient compliance Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Gums prevent the sedimentation of dispersed particles in manufacturing process. Collapse protectants like gelatin prevents the shrinkage of Zydis units during freeze-drying process or on long term storage. The product is very light weight and fragile, and must be dispensed in a special blister pack [17].

4.2 Orasolv Technology

Orasolv was Cima's first fast disintegrating dosage form. In this system active medicament is taste masked, contains disintegrating agent. The disintegration of FDT in the mouth is cause by the action of an effervescent agent, activated by saliva. The amount of effervescent agent is in general about 20-25% of the total weight of the tablet. The widely used effervescent disintegration pair usually include an acid source (citric, tartaric, malic, fumeric, adipic and succinics) and a carbonate source (sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate).The major disadvantage of the Orasolv formulations is its mechanical

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strength. For that reason, Cima developed a special handling and packaging system for Orasolv. Manufacturing requires a controlled environment at low relative humidity and protection of the final tablets with moisture impermeable blisters [18].

4.3 Durasolv Technology

Durasolv is Cima's second generation fast dissolving or disintegrating tablet formulation to produce stronger tablets for packing in conventional blisters or bottles. Durasolv has much higher mechanical strength due to use of the higher compaction pressure during tabletting. One disadvantage of Durasolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to high pressure during compaction. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter tasting drugs to the patient taste buds. So this technology is good for tablets having low amount of active ingredients [19].

Table 3. Name of patented technologies for preparation of FDTs and basic process for each patented technology

S.No.	Patented Technologies for FDTs	Basic Process
1.	Zydis®	Lyophilization
2.	Quicksolv®	Lyophilization
3.	Nanocrystal Technology®/ Nanomelt	Lyophilization
4.	Lyoc®	Lyophilization
5.	Sheaform Technology®	Cotton Candy Process
6.	Flashdose®	Cotton Candy Process
7.	Ceform Technology®	Microspheres and Compression
8.	OraQuick®	Micromask Taste Masking
9.	Dispersible Tablet Technology®	Direct Compression
10.	Pharmaburst technology®	Direct Compression
11.	Frosta ®	Direct Compression
12.	Ziplets®	Direct Compression
13.	Wowtab®	Direct Compression
14.	Durasolv®	Direct Compression
15.	Orasolv®	Direct Compression
16.	Flashtab®	Direct Compression

4.4 Wow Tab Technology

The WOW in the WOWTAB signifies the tablet is to be given without water. This technology utilizes sugar and sugar-like excipients. The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. The two different saccharides are those with high moldability like maltose, mannitol, sorbitol, and oligosaccharides (good binding property) and low moldability like lactose, glucose, mannitol, xylitol (rapid dissolution). Tablets produced from this technology will have sufficient hardness to maintain the physical characteristics of the dosage form during production until it comes in contact with moisture such as saliva in mouth. Due to the significant hardness the WOWTAB formulation is more stable to the environment than the Zydis and Orasolv. Erythritol was found to be the best sugar for this type of formulation, showing rapid disintegration which is unaffected by tablet hardness [20].

4.5 Oraquick Technology

The Oraquick fast dissolving/disintegrating tablets formulation utilizes a patented taste masking technology. This taste masking process does not utilize solvents of any kind, so leads to faster and more efficient production. During processing low-heat is produced so this technique is suitable for heat sensitive drugs. KV pharmaceuticals also claim that the matrix that surrounds and protects the drug powder in microencapsulated particle is more pliable. This technique gives tablets with good taste masking and quick dissolution in matter of seconds.

4.6 Nanocrystal Technology

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

4.7 Shear form Technology

In this technology, a shear form matrix, 'Floss' is prepared. Feedstock prepared with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass. This is followed by its exit through the spinning head that flings the floss under centrifugal force and draws into long and thin floss fibres, which are usually amorphous in nature. The floss so produced, is further chopped and recrystallised to provide a uniform flow, thus facilitate blending. Then the recrystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the floss before recrystallising it. The tablets manufactured by this process are highly porous in nature and

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offer very pleasant mouth feel due to rapid solubilisation of sugars in presence of saliva [21].

4.8 Pharma Burst Technology

Pharmaburst technology is patented by SPI pharma. Pharma burst technology uses off the shelf coprocessed excipients to create an FDT that, depending on the type of active ingredients and loading, dissolves within 30- 40 seconds. The quantity of pharma burst required in a formulation depends on the active ingredients in the tablet. The process involves a dry blend of a drug, flavor and lubricant that are compressed into a tablet on a standard tablet press with stock tooling. The manufacture process can be carried out under normal temperature and humidity conditions. The tablets can be packaged in blister packs or bottle [22].

4.9 Frosta Technology

Akina patents this technology. The core concept of Frosta technology is compressing highly plastic granules at low pressure to produce strong tablets with high porosity. The highly plastic granules comprise three classes of components: a porous and plastic material, a water penetration enhancer, and a binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The technology can be used for almost any drugs including aspirin, loratidine, caffeine and folic acid, vitamins and dietary supplements. The highly plastic granule approach produces fast melting pharmaceutical tablets with excellent hardness and fast disintegration time ranging from several seconds to 30 seconds, depending on the size of the tablets [23].

5. EVALUATION OF PREPARED TABLETS

Tablets from all the formulation were subjected to following quality control test.

5.1 General Appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. It includes tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

5.2 Size and Shape

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

5.3 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.

5.4 Uniformity of Weight

As per I.P. procedure for uniformity of weight was followed, twenty 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.

Table 4. Uniformity of weight

S.No.	Average Weight of Tablets (mg)	Maximum Percentage different Allowed
1.	130 or less	10
2.	130-324	7.5
3.	More than 324	5

5.5 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 Monsato Hardness tester.

5.6 Friability

It is the measurement of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A preweighed 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 percentage as,

$$\% \text{ Friability} = \text{Loss in weight} / \text{Initial weight} \times 100 \quad \ldots\ldots (1)$$

5.7 *In-vivo* Disintegration Test

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37°C ± 2°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds [24].

5.8 *In vitro* Dispersion Time

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

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Table 5. FDT Product in Indian and International Market [25]

Indian Market			International Market		
Brand Name	**Ingredients**	**Company**	**Brand Name**	**Ingredients**	**Company**
Sulbid	Nimesulide	Alpic Remedies	Zyprexa	Olanzepine	Eli Lilly
Olnium MD	Nimesulide	Olcare Lab	Fluoxetine ODT	Fluoxetine	Biovail
Nisure MD	Nimesulide	Suzen Pharma	Zolpidem ODT	Zolpidem tartrate	Biovail
Nimex MD	Nimesulide	Mexon healthcare	Excedrin Quick Tabs	Acetaminophen	Bristol-Myers Squibb
Nexus MD	Nimesulide	Lexus	Gaster D	Famotidine	Yamanouchi
Orthoret MD	Rofecoxib	Biochem	Nasea OD	Ramosetoron HCl	Yamanouchi
Zilflam	Rofecoxib	Kapron	Benadryl Fast Melt	Diphenhydramine Citrate	Pfizer
Dolib MD	Rofecoxib	Panacea	Kemstro	Baclofen	Schwarz Pharma
Rofaday MT	Rofecoxib	Lupin	NuLev	Hyoscyamine Sulfate	Schwarz Pharma
Torrox MT	Rofecoxib	Torrent	Alavert	Loratadine	Wyeth Consumer Healthcare
Valus	Valdecoxib	Glenmark	Zomig-ZMT and Rapimelt	Zolmitriptan	Astra Zeneca
Olanexinstab	Olanzepine	Ranbaxy	Propulsid Quick Sol	Cisapride monohydrate	Janssen
Manza BDT	Olanzepine	Orchid	Risperdal M Tab	Risperidone	Janssen
Romilast	Montelukast	Ranbaxy	Zofran ODT	Ondansetron	Glaxo Smithkline
Remeron Sol Tab	Mirtazapine	Organon	Cibalginadue Fast	Ibuprofen	Novartis Consumer Health
Maxalt ODT	Famotidine	Merck	Hyoscyamine sulfate ODT	Hyoscyamine sulfate	Ethex Corporation
Feledine Melt	Piroxicam	Pfizer	Nurofen Flashtab	Ibuprofen	Boot healthcare
MOSID-MD	Mosapride Citrate	Torrent Pharmaceuticals	Calritin Reditabs	Calritin	Schering Plough, U.S.A
Nimulid-MD	Nimesulide	Panacea Biotech	Pepcidin	Rapitab Pepcid	Merck & Co., U.S.A
Zyrof meltab	Rofecoxib	Zydus Cadila	Nimpain MD	Nimesulide	Prompt cure Pharma

5.9 Moisture Uptake Studies

Moisture Uptake Studies for FDT should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic. Ten tablets from each formulation are kept in a desiccator over calcium chloride at 37°C for 24 h. The tablets are then weighed and exposed to 75% RH at room temperature for two weeks. The required humidity (75% RH) is achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days. One tablet as control (without superdisintegrant) is kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded.

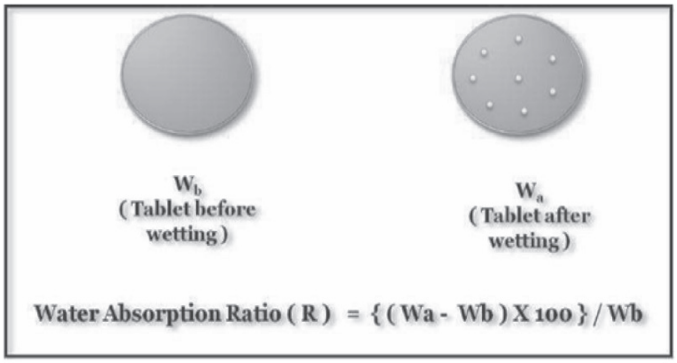

Fig. 6. Water absorption process

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5.10 Wetting Time and Water Absorption Ratio

A piece of whatman filter paper folded twice was kept in a petridish (internal diameter 4 cm) containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. When the upper surface of the tablet acquires a red colour, the time was recorded as wetting time. The same procedure without using Rosaline dye was determined according to the following equation [26].

5.11 Dissolution Test

The development of dissolution methods for FDTs is comparable to the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent FDT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for FDT much in the same way as their ordinary tablet counterparts. It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used [27].

5.12 Clinical Studies

In vivo studies have been performed on oral fast-disintegrating dosage forms to investigate their behavior in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. Zydis's residence time in the mouth and stomach, and its transit through the esophageal tract, was investigated using gamma-scintigraphy. Its dissolution and buccal clearance was rapid, the esophageal transit time and stomach emptying time were comparable with those of traditional tablets, capsules, or liquid forms. A decreased intersubject variability in transit time was also observed. Zydis also showed good therapeutic efficacy and patient acceptability – particularly in children or when easy administration and rapid onset of action were required (such as for patients undergoing surgery). The fast disintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. For example, the absorption rate of the acetaminophen Flashtab was higher than that of the brand leader, while having the same bioavailability. Increased bioavailability and improved patient compliance were observed in Lyoc formulations for different drugs such as phloroglucinol, glafenine, spironolactone, and propyphenazone. Using Zydis, all the drugs that can be absorbed through the buccal and esophageal mucosa exhibited increased bioavailability and side-effect reduction. This is helpful particularly in actives with marked first-pass hepatic metabolism. Finally, the suitability of FDTs for long-term therapy was also assessed. Lyoc formulations containing aluminum were positively tested in patients with gastrointestinal symptoms.

5.13 Stability Testing of Drug (Temperature Dependent Stability Studies)

The fast dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

- 40 ± 1°C
- 50 ± 1°c
- 37 ±1°C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C [28, 29].

6. PATIENTS COUNSELING POINTS FOR FDDTS

Pharmacists are in the ideal position to become familiar with the different technologies, and educate their patients on what to expect upon taking their first dose.

- Patients may be surprised when tablets begin to dissolve in the mouth.
- They might expect a faster onset of therapeutic action.
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- Similarly, patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.
- Although no water is needed to allow the drug to disperse quickly and efficiently, most technologies utilize the body's own salivation.
- Decreased volume of saliva may slow the rate of dissolution/disintegration and decrease the bioavailability of the product.
- Chewable tablets are not the same as the new FDDTs. Patients for whom chewing is difficult or painful can use these new tablets easily. FDDTs can be used easily in children who have lost their primary teeth, but do not have full use of their permanent teeth.
- Patients may mistake fast-dissolving/disintegrating for effervescent tablets. Pharmacists may wish to stress the difference between the use of quick-dissolving and effervescent tablets.
- Pharmacists have been alerted to exercise additional care when dispensing new prescriptions for FDDT formulations. Most such products are available in the same strengths as traditional dosage forms.

- Verification with the prescribing practitioner may be necessary in some cases and can clear up any confusion.
- Pharmacists may wish to consider compounding as a unique way to treat the unmet needs of individual patients.
- A pharmacist's intervention and assistance, all of these patients could be more properly treated with greater convenience.

7. FUTURE PROSPECTS

These dosage forms may be suitable for the oral delivery of poorly water soluble drugs, protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. It may be possible that next generation drugs would be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by FDTs which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight protein and peptide.

8. CONCLUSION

FDT concept evolved to overcome some of the problems that existed in conventional solid dosage form i.e. difficulty in swallowing of tablet in pediatric and geriatric patients, who constitute a large proportion of world's population. FDT may lead to improve efficacy, bioavailability, rapid onset of action, better patient compliance and better safety compared with conventional oral dosage forms due to its quick absorption from mouth to GIT as the saliva passes. Prescription FDT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia. At present time, FDTs are more widely available as OTC products for the treatment of allergies, cold, and flu symptoms. The target patient has expanded to those who want convenient dosing anywhere, anytime, without water. The research on FDTs should be focused on decreasing the dissolution time of the tablets in the mouth, while maintaining sufficiently high mechanical strength to withstand handling during manufacturing, packaging and transportation. Hence it can be concluded that using a combination of modified technique and suitable excipient would be quite effective in providing faster onset of action without the need of water for swallowing of fast dissolving tablets.

REFERENCES

[1] Bhowmik, D.; Chiranjib.B,; Krishnakanth; P.; Chandira, R.M. Fast Dissolving Tablet: An Overview. *Journal of Chemical and Pharmaceutical Research*. 2009, 1(1), 163-177.

[2] Heer, D.; Aggarwal, G.; Kumar, S.L.H. Recent Trends of Fast Dissolving Drug Delivery System – an Overview of Formulation Technology. *Pharmacophore*. 2013, 4 (1), 1-9.

[3] Jain, C.P.; Naruka, P.S. Formulation and evaluation of fast dissolving tablets of Valsartan. *International Journal Of Pharmacy And Pharmaceutical Sciences*. 2009, 1(1), 219-226.

[4] Gupta, A.K.; Mittal, A.; Jha, K.K. Fast Dissolving Tablet – A Review. *The Pharma Innovation*.2012, 1(1), 1-8.

[5] Nautiyal, U.; Singh,S.; Singh, R.; Gopal; Kakar, S. Fast Dissolving Tablets as A Novel Boon: A Review. *Journal of Pharmaceutical, Chemical and Biological Sciences*. 2014, 2(1), 05-26.

[6] Thakur, N.; Bansal, M.; Sharma, N.; Yadav, G.; Khare, P. Overview "A Novel Approach of Fast Dissolving Films and Their Patients". *Advances in Biological Research*. 2013, 7 (2), 50-58.

[7] Verma, A. K.; Sachan, A. K. A review on fast dissolving tablet as an efficient technique for oral drug delivery. *Journal of Chemical and Pharmaceutical Sciences*. 2013, 6(1), 29- 34.

[8] Panigrahi, R.; Behera, S.; Panda, C. A. Review on Fast Dissolving Tablets. *Webmed Central*. 2011, 2-15.

[9] Shaikh, S.; Khirsagar, R.V.; Quazi, A. Fast disintegrating tablets: an overview of formulation and technology. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2010, 2(3), 9-15.

[10] Mangal, M.; Thakur, N,; Bansal, R.; Thakral, S.; Goswami, M. Fast dissolving tablet: an approach for emergency treatment. *International Journal of Research in Ayurveda and Pharmacy*. 2012, 3(3), 377-380.

[11] Gupta, D. K.; Bajpai, M.; Chatterjee, D.P. Fast mouth dissolving disintegrating tablet and patient counselling points for FDDTs – a review. *International Journal of Research and Development in Pharmacy and Life Sciences*. 2014, 3(3), 949-958.

[12] Venkateswarlu, B.; Kumar, B.P.; Bowmik, D. Formulation and evaluation of Famotidine fast dissolving tablets by direct compression method. *Indian Journal of Research in Pharmacy and Biotechnology*. 2013, 1(5), 609-613.

[13] Yapar, E.A. Orally disintegrating tablets: an overview. *Journal of Applied Pharmaceutical Science*. 2014, 4(2), 118-125.

[14] Panda, B.P.; Dey, N.S.; Rao, M.E.B. Development of innovative orally fast disintegrating film dosage forms: a review. *International Journal of Pharmaceutical Sciences and Nanotechnology*. 2012, 5(2), 1666-1674

[15] Lokesh, P.N.V.; Abdul, A.S.; Sailaja, P.B. Design, development and formulation of orodispersible tablets of a model drug using response surface methodology. *Pharmaceut Anal Acta*. 2012, 3(9), 1-15.

[16] Parashar, B.; Yadav, V.; Maurya, B.; Sharma, L. Fast dissolving tablet. *International Journal of Applied Pharmaceutics*. 2012, 4(2), 17-22.

[17] More, S.; Ghadge, T. Fast disintegrating tablets: an overview. *Asian Pharma Press*. 2013, 3(2), 47-55.

[18] Bhushan, V.; Singh, M.; Chauhan, A. A review on evaluation and formulation of fast dissolving tablets. *International Journal of Drug Research and Technology*. 2011, 1 (1), 8-16.

[19] Gupta, A.K.; Mittal, A.; Jha, K.K. Fast dissolving tablet- A review. *The Pharma Innovation*. 2012, 1(1), 1-8.

[20] Hirani, J. J.; Rathod, D.A.; Vadalia, K.R. Orally disintegrating tablets: a review. *Tropical Journal of Pharmaceutical Research*. 2009, 8 (2), 161-172.

[21] Desale, K.Y.; Vidhyadhar, H.; Bankar; Preeti, D.; Gaikwad; Sunil, P.; Pawar. Review on: fast dissolving/disintegrating tablets. *International Journal of Pharmaceutical Sciences Review and Research*. 2011, 11 (1), 152-158.

[22] Kaur, T.; Gill, B.; Kumar, S.; Gupta, G.D. Mouth dissolving tablets: a novel approach to drug delivery. *International Journal of Current Pharmaceutical Research*. 2011, 3(1), 1-7.

[23] Kumar, E.; Joshi, B. Mouth Dissolving Tablets – A Comprehensive Review. *International Journal of Pharma Research & Review*. 2013, 2(7), 25-41.

[24] Prasanthi, N.L.; Manikiran, S.S.; Rao, N.R. Formulation and characterization of fast-dissolving tablets of Raloxifene Hydrochloride. *International Journal of Pharmaceutical Sciences and Drug Research*. 2010, 2(1), 55-57.

[25] Velmurugan, S.; Vinushitha, S. Oral disintegrating tablets: an overview. *International Journal of Chemical and Pharmaceutical Sciences*. 2010, Vol. 1 (2), 1-12.

[26] Ashish, P.; Harsoliya, M.S.; Pathan, J.K.; Shruti, S. A review-formulation of mouth dissolving tablet. *International Journal of Pharmaceutical and Clinical Science*. 2011, 1(1), 1-8.

[27] Sachan, A.K.; Tripathi, K.; Visnoi, G.; Rasheed, A.; Sharma, R.; Gangwar, S.S. Formulation development and characterization of Piroxicam fast dissolving tablets approved for the treatment of arthritis. *International Journal of Development Research*. February 2015, 5(2), 3440-3446.

[28] Sachan, A.K.; Tripathi, K.; Sachan, P.; Gangwar, S.S. Fabrication and characterization of compressed solid dispersion based fast dissolving tablets of sildenafil citrate. *International Journal of Pharmaceutical Sciences Review and Research*. January – February 2015, 30(1), 98-104.

[29] Sachan, A.K.; Gupta, A.; Nigam, L.; Sharma, R.; Gangwar, S.S. Design and characterization of solid dispersion based fast dissolving tablet of Cetirizine hydrochloride. *MIT International Journal of Pharmaceutical Sciences*. January 2015, 1(1), 37–44.