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Review Article

FAST DISSOLVING DRUG DELIVERY SYSTEM - A REVIEW

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ABSTRACT
Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after administration. Drug delivery systems are becoming sophisticated day by day as pharmaceutical scientists has acquired a better understanding of the physicochemical and biochemical parameters of drugs and excipients. Over the past three decades, fast disintegrating tablets (FDTs) have gained considerable attention and is one of the most widely employed commercial product which is preferred alternative to conventional tablets and capsules especially for the pediatric and geriatric patients and for the patients who are bedridden, those having hand tremors, motion sickness, dysphagia and who may not have access to water during traveling or who are uncooperative, on reduced liquid intake plan and also preferred in sudden episodes of allergic attack. Fast-dissolving drug delivery systems may offer a solution for these problems.

KEY WORDS: Fast dissolving drug delivery system, Super-Disintegrants, Conventional techniques, Patented technology, Excipients used in FDDTs, Evaluation of FDDTs

INTRODUCTION

There has been an enhanced demand for more patient-convenient and compliant dosage forms in market for the past few decades, because of which the demand for developing new technologies has been increasing day by day[1]. As the development cost of a new drug molecule is very high, efforts have been made by pharmaceutical companies and researchers to focus on the development of new drug dosage forms for existing one having improved safety and efficacy with reduced dosing frequency, and more cost effective dosage forms. For most therapeutic agents used to produce systemic effects, the oral route represents the most preferred way of administration because of its several advantages and high patient compliance compared to other routes[2]. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Should next generation drugs are predominantly protein or peptide based, tablets may no longer may be the dominant format give the difficulty of dosing such moiety. 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 generate predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide[3,4,5,6,7,8,9,10]. Recent advances in Novel Drug Delivery Systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop a Fast Dissolving Drug Delivery System[11]. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus 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. FDDTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms.[12,13]

The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."
The oral fast-disintegrating tablets are also known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar.[14]

Biopharmaceutic Consideration

When new drug delivery system put on, it is must that to consider Biopharmaceutical factor like metabolism and excretion[15].

Pharmacokinetics

In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution while FDT is rapidly disintegrates in oral cavity and dissolution is fast. Due to disintegration of FDT in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders may be considered as separate unique Medicare population. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. In geriatric patients, decrease in body mass and total body water result in decreased volume of distribution of water-soluble drugs and increased volume of distribution (Vd) of lipid soluble drugs. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamic

Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ. Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.

1. Decreased sensitivity of the CVS to -adrenergic agonist and antagonist.
2. Immunity is less and taken into consideration while administered antibiotics.

3. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.
4. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed. Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patient.

Advantages Of Fast Dissolving Tablets

1. FDT can be administer to the patients who can not swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. Rapid drug therapy is possible.
3. Certain studies concluded increased bioavailability/proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
4. FDT are convenient for administration and passes good patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
5. Good mouth feel property of FDT helps to change the perception of medication as bitter pill particularly in pediatric patients.
6. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
7. FDT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management[16].

Limitations To Fast Dissolving Tablets

1. Drugs with relatively larger doses are difficult to formulate into FDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
2. Patients who concurrently take anticholinergic medications may not be the best candidates for FDT. 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[17].

The Need For Development Of FDTS

Patient factors

Orally disintegrating dosage forms are exceptionally suitable for patients, who find solid dosage form inconvenient to swallow with a glass of water. These patients are the following:

1. Pediatric and geriatric patients having difficulty in swallowing or chewing solid dosage forms
2. Patients who are reluctant to take solid preparation due to fear of choking
3. Patient with allergies who requires a more convenient dosage form than antihistamine syrup
4. A middle-aged woman subjected to radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker dose.
5. A schizophrenic patient who may try to hide a conventional tablet under his or her tongue so as to avoid their daily dose of an atypical antipsychotic.
6. A patient with motion sickness during the journey may have little or no access to water[18-21].

Effectiveness factor

The major call for these formulations is increased bioavailability and faster onset of action. In some cases, where drug dissolves quickly its dispersion in saliva in oral cavity causes pregastric absorption from some formulations in Buccal, pharyngeal and gastric regions[22]. A pregastric absorption avoids first pass metabolism and it is advantageous to drugs that undergo first pass hepatic metabolism. Correspondingly, safety profiles may be improved for drugs which produce substantial toxic metabolites by first-pass hepatic metabolism and gastric metabolism[23].

Manufacturing and marketing factors

Emerging new drug delivery technologies and utilizing them in new product development is crucial for pharmaceutical industries to survive, nevertheless of its size. It is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form as a drug nears the end of its patent life. A new dosage form allows a manufacturer to extend market exclusively. It provides unique product differentiation, and extends patent protection, henceforth offering its patient population a more convenient dosage form[24]. For instance Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M (simvastatin ODT), a line extension of its block-buster, Zocor, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2004.[25]

Ideal Drug Candidates Of Fast Dissolving Tablets

1. Fast dissolving tablets Dose should be lower than 20 mg;
2. Drug should be partially non ionized at pH in oral cavity's.
3. Drug should be diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferably >2)
4. Drug should have to permeate through oral mucosal tissue.[26,27]

Ideal Characteristics Of Fast Dissolving Delivery System

Mouth-feel[28]: Mouth-feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can an improved mouth-feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth-feel by reducing the "dryness" of a product.

Hygroscopicity: Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence they need protection from humidity, which calls for specialized product packaging.

Friability: In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either 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 packing. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets, such as Wowtab by Yamanouchi-Shadlee and Dura Solve by CIMA labs.

Palatability: Most orally disintegrating drug delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient complian[29,30].

Size of tablet: It has been reported that the easiest size of tablet to swallow is 7-8 mm 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[31].

Potential Candidate For FDT

Analgesics and Anti-inflammatory Agents: Aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofencalcim, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamicacid, nabumetone, naproxen, oxaprozin,oxyphenbutazone, phenylbutazone,piroxicam, sulindac.

Anthelmintics : Albendazole, bepheniumhydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole,

oxamniquine, oxfendazole, oxantelembonate, praziquantel, pyrantelembonate, thiabendazole.

Anti-Arrhythmic Agents: AmiodaroneHCl, Disopyramide, flecainideacetate,quinidinesulphate.

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.

Anti-coagulants: Dicoumarol, dipyridamole, nicoumalone, phenindione.

Anti-depressants: Amoxapine, ciclazindol, maprotilineHCl, mianserinHCl, nortriptylineHCl, trazodoneHCl, trimipramine maleate.

Anti-diabetics: Acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide.

Anti-epileptics: Beclamide, carbamazepine, clonazepam, ethotoin, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, valproic acid.

Anti-fungal Agents : Amphotericin, butoconazolenitrate, clotrimazole, econazolenitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafineHCl, terconazole, tioconazole, undecenoic acid.

Anti-gout Agents: Allopurinol, probenecid, sulphinpyrazone.

Anti-hypertensive Agents: Amlodipine, carvedilol, benidipine, darodipine, dilitazemHCl, diazoxide, felodipine, guanabenz acetate, indoramin, isradipine, minoxidil, nicardipineHCl, nifedipine, nimodipine, phenoxybenzamineHCl, prazosin HCL, reserpine, terazosin HCl.

Anti-malarials: Amodiaquine, chloroquine, chlorproguanilHCl, halofantrineHCl, mefloquineHCl, proguanilHCl, pyrimethamine, quinine sulphate.

Anti-migraine Agents: Dihydroergotaninemesylate, ergotamine tartrate, methysergidemaleate, pizotifen maleate, sumatriptan succinate.

Anti-muscarinic Agents: Atropine, benzhexolHCl,biperiden, ethopropazineHCl, hyoscine butyl bromide, hyoscyamine, mepenzolatebromide,orphenadrine, oxyphencylcimineHCl, tropicamide.

Anti-neoplastic Agents and Immunosuppressants: Aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazineHCl, tamoxifen citrate, testolactone.

Anti-protazoal Agents: Benznidazole, clioquinol, decoquinate, diiodohydroxyquinoline, diloxanidefuroate, dinitolmide, furzolidone, metronidazole, nimorazole, nitrofurazone, omidazole, tinidazole.

Anti-thyroid Agents: Carbimazole, propylthiouracil.

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, flupenthixoldecanoate, fluphenazinedecanoate, flurazepam, haloperidol.

Cardiac InotropicAgents: Amrinone, digitoxin,digoxin, enoximone, lanatoside C, medigoxin.

Corticosteroids: Beclomethasone, betamethasone, budesonide,cortisone acetate, desoxymethasone, dexamethasone, fludrocortisoneacetate, flunisolide, flucortolone,fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone,prednisone, triamcinolone.

Diuretics: Acetazolamideamiloride, bendroflnazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynicacid,frusemide, metolazone, spironolactone, triamterene.

Enzymes: All the enzymes.

Anti-parkinsonianAgents: Bromocriptinemesylate, lysuride maleate.

Gastro-intestinal Agents: Bisacodyl, cimetidine, cisapride, diphenoxylateHCl, domperidone, famotidine, loperamide, mesalazine,nizatidine, omeprazole, ondansetron HCL, ranitidine HCl, sulphasalazine

Histamine H,-Receptor Antagonists: Acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadineHCl, dimenhydrinate, flunarizineHCl, loratadine, meclozineHCl, oxatomide, terfenadine, triprolidine.

Lipid Regulating Agents: Bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol.

Local Anaesthetics: Lidocaine

Neuro-muscular Agents: Pyridostigmine.

Nitrates and other Anti-anginal Agents: Amyl nitrate, glyceryltrinitrate, isosorbidedinitrate, isosorbidemononitrate, pentaerythritoltetranitrate.

Nutritional Agents: Betacarotene, vitamin A, vitamin B2, vitamin D,vitamin E, vitamin K.

Opioid Analgesics: codeine, dextropropyoxyphene, diamorphine, dihydrocodeine, meptazinol, methadone, morphine, nalbuphine, pentazocine.

OralVaccines: Vaccines designed toprevent 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, Measles, Lyme disease, Travellers Atrophic rhinitis, Erysipelas, Foot and Mouth disease, Swine, pneumonia, andother disease conditions and other infections and auto-immune disease conditions affecting companion and farm animals.etc.

Stimulants: Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol, pemoline.[32]

Exciepients Used To Prepare FDT

Emulsifying Agents

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.[33]

Binders

Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage. Binders commonly used are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulosic polymers it will be advantageous to select ethylcellulose, hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures, and the most commonly acrylic polymers are used are the ammonio-methacrylate copolymer (Eudragit. RL and RS), polyacrylate (Eudragit. NE), and polymethacrylate (Eudragit. E). 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 30–35C for faster melting properties.[34]

Antistatic agent and Diluents

The most common antistatic agents used are colloidal silica (Aerosil), precipitated silica (Sylod.FP244), micronized or non micronized talc, maltodextrins, .beta.-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearylfumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant4. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling. Commonly used Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols, and, preferably, mannitol[35,36].

Superdisintegrants

Superdisintegrants	Example	Mechanism Of action	Special comment
Croscarmellose® Ac-Di-Sol® Nymce ZSX®	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free

Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wetability and dispersibility of the system, thus enhancing the disintegration and dissolution. [34]

Primellose®Solutab® Vivasol®L-HPC	Crosslinked PVP	-Swells very little And returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super Disintegrant	-Does not contain any starch or sugar. Used in nutritionalproducts	-

Flavours: Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptos oil thyme oil, oil of bitter almonds. Flavoring agnets include, vanilla, citus oils, fruit essences.[37,38]

Sweetners: Aspartame, Sugars derivatives[37,38]

Fillers: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.[37,38]

Surface active agents: sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylenesorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.[37,38]

Technologies Used To Manufacture Fast Dissolving Tablets

Conventional technologies

1. Freeze Drying
2. Tablet Molding
3. Spray Drying
4. Direct Compression
5. Sublimation
6. Cotton Candy Process
7. Mass Extrusion[24]

Patented technologies

1. Zydis Technology
2. Durasolv Technology
3. Orasolv Technology
4. Wowtab Technology
5. Flashdose Technology
6. Flashtab Technology

Freeze drying

Freeze-drying allows immediate dissolution of the tablets because of their high porosity, and enhances drug stability, especially for moisture-sensitive substances; on the other hand, a porous network is associated with low physical resistance and high friability. Special packaging is required in some cases.[39]

Advantages of freeze drying

The major advantage is that the tablets produced by this technology have very low disintegration time and have great mouth feel due to fast melting effect.[40]

Disadvantages of freeze drying

Although being a fairly routine process, lyophilization has some disadvantages like it is relatively expensive and time consuming process. Furthermore, the product obtained is poorly stable and fragile, rendering conventional packaging unsuitable. Very poor physical resistance, High cost of production, Low dose of water soluble drugs.[40]

Tablet Molding

Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in 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 posses 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 30^0C 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. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.[41]

Spray drying

The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g..citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 secs in an aqueous medium.[42]

Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production method.

Advantages of direct compression

1.Requires fewer unit operations compared with wet Granulation (shorter processing time and lower energy consumption).

2.Fewer stability issues for actives that are sensitive to heator moisture.

3.For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, norfloxacin.

4.Fewer excipients may be needed in a direct compression formula. [43]

Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate, hexamethelenetetramine, camphor etc.) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation (Fig. 1), which generates porous structures. Additionally, several solvents (e.g. cyclohexane, benzene) can be also used as pore forming agents. [44]

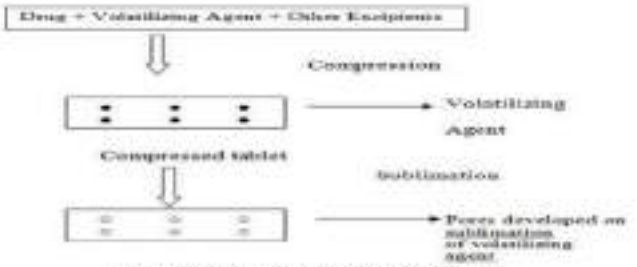

Figure 1 Various steps involve in sublimation

Cotton Candy Process

This process is so named as it utilizes a unique spinning mechanism to produce floss like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT. This process can accommodate larger drug doses and offers improved mechanical strength. However, high-process temperature limits the use of this process. [45]

Mass extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste. [46]

IMPORTANT PATENTED TECHNOLOGIES FOR FAST DISSOLVING TABLETS

Zydis Technology[47,48]

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These forms a glossy amorphous structure, which imparts strength.

To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

Limitations

1. The amount of drug could be incorporated should generally be less than 400mg for insoluble drugs and less that 60mg for soluble drugs.
2. The particle size of the insoluble drugs should not be less than 50µm and not more than 200µm to prevent sedimentation during processing.

Advantages

1. Buccal pharyngeal and gastric regions are all areas of absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that udergo a great deal of hepatic metabolism.
2. The zydis formulation self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

Disadvantages

1. The process of freeze-drying is a relatively expensive manufacturing process.
2. The formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses.
3. It has poor stability at higher temperatures and humidities.
4. The freeze-drying is time consuming process
5. It has poor physical resistance
6. Loading of high dose of water-soluble drugs is not possible

Durasolv Technology[47, 48]

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

Advantages

1. Durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tabletting.
2. The Durasolv product is thus produced in a faster and in more effective manner.

Disadvantages

1. It is not compatible with larger doses of active ingredients because the formulation is subjected to high pressures on compaction.
2. The drug powder coating may fractured during compaction, exposing the bitter tasting drug to patient's taste buds.

Orasolv Technology[47, 48]

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

Advantages

1. The Orosolv formulations are not very hygroscopic
2. The formulation can accommodate high doses.
3. It also provides a distinct, pleasant sensation of effervescence in the mouth.

Disadvantages

1. A weaker and more brittle tablet in comparison with conventional tablets.
2. Poor mechanical strength.
3. The cost of fast dissolving tablets is higher than the cost of standard tablets made by direct compression
4. Manufacturing requires a controlled environment at low relative humidity.

Wowtab Technology[47, 48]

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

Advantages

1. Offers Superior mouthfeel due to the smooth melt action
2. It is suitable for both conventional bottle and blister packaging
3. it more stable to the environment than the zydis and orasolv.

Flash Dose Technology[47, 48]

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.

Flashtab Technology[47, 48]

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion- spheronisation. All the processing utilized conventional tabletting technology.

Table 2: List Of Marketed Fast Dissolving Tablets[49, 50]

S. No.	Trade Name	Active Drug	Manufacturer
1.	Felden fast melt	Piroxicam	Pfizer Inc., NY, USA
2.	Claritin redi Tab	Loratidine	Schering plough Corp., USA
3.	Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
4.	Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
5.	Pepcid RPD	Famotidine	Merck and Co., NJ, USA
6.	Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
7.	Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
8.	Zeplar TM	Selegiline	Amaran Corp., London, UK
9.	Tempes Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
10.	Febrectol	Paracetamol	Prographarm, Chateauneuf, France
11.	Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
12.	Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
13.	Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
14.	Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
15.	Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA
16.	Propulsid Quicksolv	Cisapride monohydrate	Janssen pharmaceutics
17.	Risperdal MTab	Risperidone	Janssen pharmaceutics
18.	Spasfon Lyoc)	Phloroglucinol Hydrate	Formulyoc
19.	Nurofen FlashTab)	Ibuprofen	Ethypharm
20.	Tempra Quicklets	Paracetamol	Cima Labs,Inc.
21.	Zolmig Repmelt	Zolmitriptan	Cima Labs,Inc.
22.	(NuLev	Hyoscyamine Sulfate	Cima Labs, Inc.
23.	Gaster D)	Famotidine	Yamanouchi Pharma Tech. Inc.
24.	Cibalgina DueFast	Ibuprofen	Eurand International

25.	Relivia Flash dose	Tramadol HCl	Fusz Technology, Ltd.
26.	Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharm.Co.,Inc.
27.	Abilify Discmelt	Aripiprazole	Otsuka America/Bristol-Myers Squibb
28.	Allegra ODT	Fexofenadine	Sanofi Aventis
29.	Aricept ODT	Donepezil	Eisai Co.
30.	Clarinex RediTabs	Desloratadine	Schering-Plough
31.	Alavert Quick Dissolving Tablets	Loratadine	Wyeth
32.	Clonazepam ODT	Clonazepam	Par Pharmaceutical
33.	FazaClo	Clozapine	AzurPharma
34.	Jr. Tylenol Meltaways	Acetaminophen	McNeil Consumer Healthcare
35.	Klonopin Wafers[28]	Clonazepam	Roche
36.	Loratadine Redidose	Loratadine	Ranbaxy
37.	Mirtazapine ODT	Mirtazapine	Teva Pharmaceuticals
38.	Nasivian	Alprazolam	Schwarz Pharma
39.	Ondansetron ODT	Ondansetron	Teva Pharmaceuticals
40.	Orapred ODT	Prednisolone	Sciele Pharma
41.	Parcopa	Carbidopa/levodopa	Schwarz Pharma
42.	Prevacid SoluTab	Lansoprazole	Takeda Pharmaceuticals
43.	Remeron SolTab	Mirtazapine	Schering-Plough
44.	Risperdal M-Tab	Risperidone	Janssen
45.	UNISOM SleepMelts	Diphenhydramine	Chattem
46.	Zomig-ZMT	Zolmitriptan	AstraZeneca
47.	Zyprexa Zydis	Olanzapine	Eli Lilly and Company
48.	Citalopram ODT	Citalopram	Biovail
49.	Metoclopramide Zydis	Metoclopramide	Salix Pharmaceuticals
50.	Reglan ODT	Metoclopramide	Schwarz Pharma[
51.	Tramadol/Acetamino-phen ODT	Tramadol/Acetamino -phen	Biovail
52.	Zolpidem ODT	Zolpidem	Biovail

Evaluation of FDT

Bulk characterization[50,51]

Angle of Repose, Bulk Density, Bulkiness, Void Volume, Porosity, Compressibility characterstics (Carr'sand Hausner index)

Angle of Repose

The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

tan = h/r

Therefore **= tan-1 h/r**

Where = Angle of repose

h = height of the cone

r= Radius of the cone base

Angle of Repose less than 30 ° shows the free flowing of the material.

Bulk Density

Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. The particles are pack in such a way so as to leave large gaps between their surfaces 'resulting up in light powder of low bulk density. Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.

Pb=M/Vp

Where pb =Bulk Density

M = Weight of sample in gm

Bulkiness

Specific bulk volume or reciprocal of bulk density is called bulkiness or bulk. Bulkiness increases with a decrease in particle size. In mixture of material of different sizes, however the smaller particle shifts between the larger particles and tends to reduce the bulkiness. The bulkiness can be calculated by the following formula

Bulkiness= I/ pb

Where, pb = Bulk Density.

Loose bulk density

It is defined as the ratio of weight of blend in gms to the loose bulk volume (untapped volume) in cm 3 Loose bulk density is given by

Loose bulk density p u = Weight in gms / Vb

Where Vb = Bulk volume (untapped volume)

Void Volume

The volume of the spaces is known as the void volume "v" and is given by the formula

V=Vb-Vp

Where Vb = Bulk volume (volume_before tapping)

V = True volume (volume after tapping)

Porosity

The porosity ϵ of powder is defined as the ratio of void volume to the bulk volume of the packaging.

The porosity of the powder is given by

ϵ= Vb - Vp/ Vp =1- Vp/Vb

Porosity is frequently expressed in percentage and is given as

%ϵ = (1 - Vp/ Vb) X 100

The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

Percent Compressibility

It is an important measure obtained from bulk density and is defined as,

Pb=Before compressed volume, Pu=after compressed volumes

C=Pb-Pu/Pb x100

If the bed of particles is more compressible the blend will be less flowable and flowing materials.

Evaluation of Tablets[52,53,54]

General Appearance

The general appearance of tablets includes size, shape, colour, taste, odour, surface texture.

Size, Shape, Thickness and diameter

The size and shape of the tablet can be dimensionally described, monitored and controlled. Thickness of tablets is an important characteristic for 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 measured by vernier caliper.

Uniformity of weight

In Indian Pharmacopoeia procedure for uniformity of weight was followed, ten or 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.

Hardness of Tablets

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.

Friability of tablets

Fribrater 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 fribrater 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

%Friability = intial weight- final weight/intial weight x 100

Wetting time

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

Disintegration time

As described in pharmacopoeia, tablets are placed in the disintegration tubes and time is noted. According to the European pharmacopoeia, the fast disintegrating or Orodispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen. However, it is difficult to assess the disintegration rate even in small amounts of water. Further,the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus, the disintegration rate obtained from conventional test does not appearto reflect the actual disintegration rate in human mouth. To overcome these problems, several new methods have been proposed. One of these methods uses a Charge Couple Device (CCD) camera or texture analyzer to evaluate the disintegration time of tablets. In another method, a modified DT apparatus is used. Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the liquid that it contains only 6 ml of the liquid. The assembly is supported with a heater to maintain temperature at 37°C and a magnetic stirrer. DT is noted at 25 rpm.One of the simplest methods is to take 6ml of simulated saliva in a measuring cylinder and place the tablet in it. The liquid is neither shaken nor stirred and DT is noted.[55]

***In vivo* disintegration time**[56]

In vivo disintegration time is determined using a panel of healthy human volunteers. The DT noted by the volunteers by placing the tablet in mouth.

***In Vitro* Dissolution Test**[57,58]

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) [Electrolab (ETC-11L) Tablet Dissolution Tester] at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as dissolution medium which maintained at 37±0.5°C. Aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals (2 min) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer (Shimadzu, Japan) by measuring the absorbance of the sample. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

Packaging[59]

Packaging special care is required during manufacturing and storage to protect the dosage of other fast-dissolving dosage forms. Quick-dispersing and/or dissolving oral delivery systems, the system can be packaged using various options, such as single pouch, blister card with multiple units, multiple unit dispenser, and continuous roll dispenser, depending on the application and marketing objectives.

CONCLUSION

Introduction of fast disintegrating dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the acceptance of Fast disintegrating tablets, which in turn prolongs the patent life of a drug. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed

innovative drug delivery systems known as fast dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.

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