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A Review on Fast Dissolving Tablets

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A Review on Fast Dissolving Tablets

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Abstract

Recently, fast-dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast-dissolving drug delivery systems may offer a solution for these problems.

Key Words: Fast Dissolving Tablet, drug delivery system

Introduction

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice .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. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form. Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way. Less frequently, they are designed to be absorbed through the buccal and esophageal mucosa as the saliva passé into the stomach. In the latter case, the bioavailability of a drug from fast dispersing formulations may be even greater than that observed for standard dosage forms.

The concept of Mouth Dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. 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 disintegrate and/or dissolve rapidly in the saliva without the need for water. 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. Taste-masking is of critical importance in the formulation of an acceptable FDDT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to overwhelm or complement the bitter taste of the drug. Current methods of taste masking in fast dissolving/ drug particles.FDTs are the disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Most of the FDDT technologies incorporate unique forms of taste masking as well. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of solid dosage forms, which increase consumer choice, for the reason of rapid disintegrate/dissolve in oral cavity within seconds and swallowed without the need of water or chewing. As tablet disintegrates in mouth this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism.

Fast dissolving drug delivery can be achieved various techniques like direct compression, wet granulation, compression moulding, volatization and freeze – drying. They involve different mechanisms like use of high amounts of hydrophilic disintegrating agents which allow the dosage forms to disintegrate quickly in the patient's mouth on contact with saliva

DEFINITION

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."

A fast dissolving tablet can be defined as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for fast dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet.

A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water. The fast disintegrating tablets are synonymous with fast dissolving tablets; melt in mouth tablets, rapimelts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets. Their growing importance was underlined recently when European pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly, before swallowing significance of this drug delivery system includes administration without water, accuracy dosage, easy portability, alternative to liquid dosage forms ideal for pediatrics' & geriatric patients and rapid onset of action.

Biopharmaceutic Consideration

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

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 baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.

Decreased sensitivity of the CVS to β-adrenergic agonist and antagonist.

Immunity is less and taken into consideration while administered antibiotics.

Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.

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.

DIFFICULTIES WITH EXISTING ORAL DOSAGE FORM

Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.

Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.

Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult.

Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications

Cost of products is main factor as parenteral formulations are most costly and discomfort.

Salient Features Of Mouth Dissolving Drug Delivery System

DESIRED CRITERIA FOR MOUTH DISSOLVING DRUG DELIVERY SYSTEM

Mouth Dissolving Tablet should-

Not require water to swallow, but it should dissolve or disintegrate in the mouth within matter of seconds.

Be compatible with taste masking

Be portable without fragility concern.

Have a pleasing mouth feel.

Leave minimal or no residue in the mouth after oral administration.

Exhibit low sensivity to environmental condition as humidity and temperature.

Be manufactured using conventional processing and packaging equipment at low cost.

Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients.

Convenience of administration and accurate dosing as compared to liquids.

No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

Good mouth feel property of MDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.

Rapid dissolution and absorption of drug, which may produce rapid onset of action.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, and in such cases bioavailability of drugs in increased.

Ability to provide advantages of liquid medication in the form of solid preparation.

Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

IDEAL CHARACTERISTICS OF FAST DISSOLVING DELIVERY SYSTEM

Mouth-feel - 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

POTENTIAL CANDIDATE FOR FDT.

Analgesics and Anti-inflammatory Agents:

Aloxiprin, auranofin,azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcim, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamicacid, nabumetone, naproxen, oxaprozin,oxyphenbutazone, phenylbutazone,piroxicam, sulindac.

Anthelmintics :

Albendazole,bephenium hydroxynaphthoate,cambendazole, dichlorophen,ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate, thiabendazole.

Anti-Arrhythmic Agents:

Amiodarone HCl, Disopyramide, flecainide acetate,quinidine sulphate.

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, maprotiline HCl, mianserin HCl, nortriptyline HCl, trazodone HCl, trimipramine maleate.

Anti-diabeticsAcetohexamide,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, terbinafine HCl, terconazole, tioconazole, undecenoic acid.

Anti-gout Agents: Allopurinol,probenecid, sulphinpyrazone.

Anti-hypertensive Agents:

Amlodipine, carvedilol, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, indoramin, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxybenzamine HCl, prazosin HCL, reserpine, terazosin HCl.

Anti-malarials:

Amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine, quinine sulphate.

Anti-migraine Agents:

Dihydroergotamine mesylate,ergotamine tartrate, methysergidemaleate, pizotifen maleate, sumatriptan succinate.

Anti-muscarinicAgents:

Atropine, benzhexol HCl,biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscyamine, mepenzolate bromide,orphenadrine, oxyphencylcimineHCl, tropicamide.

Anti-neoplasticAgents and Immunosuppressants:

Aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine HCl, tamoxifen citrate, testolactone.

Anti-protazoalAgents:

Benznidazole, clioquinol,decoquinate, diiodohydroxyquinoline,diloxanide furoate, 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, flupenthixol decanoate, fluphenazine decanoate, 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, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid,frusemide, metolazone, spironolactone, triamterene.
Enzymes: All the enzymes.
Anti-parkinsonianAgents:Bromocriptine mesylate,lysuride maleate.
Gastro-intestinal Agents:
Bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mesalazine,nizatidine, omeprazole, ondansetron HCL,ranitidine HCl, sulphasalazine
Histamine H,-Receptor Antagonists:
Acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine HCl, dimenhydrinate, flunarizine HCl, loratadine, meclozine HCl, oxatomide, terfenadine, triprolidine.
Lipid Regulating Agents:
Bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol.
Local Anaesthetics : Lidocaine
Neuro-muscular Agents: Pyridostigmine.
Nitrates and otherAnti-anginal Agents:
Amyl nitrate, glyceryltrinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate.
NutritionalAgents:
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, TravellersAtrophic rhinitis, Erysipelas, Foot and Mouth disease, Swine, pneumonia, andother disease conditions and other infections and auto-immune diseaseconditions affecting companion and farm animals.etc.
Proteins,PeptidesandRecombinantdrugs:
Insulin, glucagon, growth hormone (somatotropin),polypeptides or their derivatives, , calcitonins and synthetic modifications thereof, enkephalins, interferons, LHRH and analogues (nafarelin, buserelin, zolidex), GHRH, secretin, bradykin antagonists, GRF, THF,TRH, ACTH analogues,IGF (insulin like growth factors),CGRP(calcitoningene related peptide), atrial natriurecticpeptide, vasopressin and analogues(DDAVP, lypressin),factor VIII, G-CSF (granulocyte-colony stimulating factor), EPO (erythropoitin).
SexHormones:
Clomiphenecitrate, danazol, ethinyloestradiol,medroxyprogesterone acetate, mestranol,methyltestosterone, norethisterone,norgestrel, oestradiol,conjugated oestrogens, progesterone,stanozolol, stiboestrol,testosterone, tibolone.
Spermicides:Nonoxynol.
Stimulants: Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol, pemoline.
Advantages of Fast Dissolving Drug Delivery System FDDTs
Fast dissolving technology offers:
Improved compliance/added convenience
No water needed
No chewing needed
Better taste
Improved stability
Suitable for controlled/sustained release actives
Allows high drug loading.
Ability to provide advantages of liquid medication in the form of solid preparation.
Adaptable and amenable to existing processing and packaging machinery
Cost- effective

OTHER EXCIPIENTS

Excipients balance the properties of the actives in fast-melting tablets. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is 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.

BULKING MATERIALS:

Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high

aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition .

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.

LUBRICANTS:

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

FLAVOURS AND SWEETENERS:

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

SUPER DISINTEGRANTS:

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the break up of the compacted mass when it is put into a fluid environment.

ADVANTAGES:

Effective in lower concentrations

Less effect on compressibility and flowability

More effective intragranularly

Some super disintegrants are:

1) Sodium Starch Glycolate (Explotab, primogel) used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action: Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking

2) Cross-linked Povidone (crospovidone) (Kollidone) used in concentration of 2-5% of weight of tablet. Completely insoluble in water.

Mechanism of Action: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other sisintegrants.

3) Low-substituted hydroxyl propyl cellulose,l which is insoluble in water. Rapidly swells in water. Grades LH-11 and LH-21 exhibit the greatest degree of swelling. Certain grades can also provide some binding properties while retaining disintegration capacity. Recommended concentration 1-5%

4) Cross linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose sodium:

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation

Gas producing disintegrants

Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other methods of improvement. Care should be taken during tab letting, particularly on moisture level. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates.

In many instances lower concentration can be used with gas producing disintegrants than are required by other disintegrating agents. Certain peroxides that release oxygen have been tried, but they do not perform as well as those releasing carbon dioxide

Conventional Technique Used In The Preparation Of MFDTS

* Freeze drying technique
* Tablet molding technique
* Spray drying technique
* Direct compression technique
* Sublimation technique
* Mass extrusion technique

Freeze Drying Technology (Zydis Technology) [20]

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth.

The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix

and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of final product. These include suspending agents, wetting agents, preservatives, antioxidants, colors and flavors. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless.

Corveleyn and Remon investigated the influence of various formulation and process parameters on the characteristics of rapidly disintegrating tablets in lyophilized form using hydrochlorthiazide as a model drug. They have concluded that maltodxtrins are useful in the formulation of fast dissolving tablets made by freeze-drying.

Lyophilization is relatively expensive and time consuming manufacturing process. Other drawback includes fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition.

Tablet Molding [20]

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet.

To overcome poor taste masking characteristic Van Scoik incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

Spray Drying [20]

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly; spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to forma highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets.

Allen et al used a spray drying technique to prepare fast dissolving tablets. The tablets made from this technology are claimed to disintegrate within 20 seconds.

Direct Compression Method [20]

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level.

Cousin et al, using carboxymethyl cellulose as disintegrating agent and one swelling agent consisting of modified starch or microcrystalline cellulose formulated rapidly disintegrable multi particular tablets. The tablets disintegrate in the mouth in less than 60 seconds.

Gas Evolving disintegrants have been used to formulate fast dissolving tablets. The evolution of carbon dioxide as a disintegration mechanism called OROSOLV and DURASOLV have been described in two US Patents assigned to CIMA Labs J. Michaelson described the use of intimate mixture of alginic acid and a water-soluble metal carbonic acid to prepare tablets. When tablet was placed in water, an acid base reaction takes place forming a metal alginic acid salt and carbonic acid. The salt caused the tablet to swell and the carbonic acid produced carbon dioxide within the swelling tablet whereby rapid disintegration of tablet was effected.

Sublimation Technique [20]

The basis of this technique is to add inert solid ingredients that volatilize readily, (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure.

Koizumi et al applied the sublimation technique to prepare highly porous compressed tablets that were rapidly soluble in saliva. Mannitol and camphor were used as a tablet matrix material and subliming the material respectively. Camphor was iminated by subliming in vacuum at 80 0C for 30 minutes to develop pores in the tablets.

Makino et al described a method of producing a fast dissolving tablet using water as a pore forming material. A mixture containing active ingredient and carbohydrates (glucose, manitol, xylitol etc) were

moistened with water (1- 3 %w/w) and compressed into tablets. The water was then removed yielding highly porous tablet that exhibited excellent ;

Mass-Extrusion(Mass-Extrusion) [20]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent 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 for bitter drugs and thereby achieve taste masking.

PATENTED TECHNOLOGIES OF FDTs [20]

Currently, four fast-dissolving/disintegrating technologies have reached the U.S. market:

* Zydis (R.P. Scherer, Inc.),
* WOWTAB (Yamanouchi Pharma Technologies, Inc.),
* OraSolv (Cima Labs, Inc.).
* DuraSolv (Cima Labs, Inc.).

Three others are available outside the U.S. :

* FlashDose (Fuisz Technologies, Ltd.),
* Flashtab (Prographarm Group),
* OraQuick (KV Pharmaceutical Co., Inc.)

Zydis Technology [20, 21]

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

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

Advantages

* 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.
* The zydis formulation self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

Disadvantages

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

Durasolv Technology [20, 21]

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

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

Disadvantages

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

Orasolv Technology [20, 21]

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

* The Orosolv formulations are not very hygroscopic

* The formulation can accommodate high doses.
* It also provides a distinct, pleasant sensation of effervescence in the mouth.

Disadvantages

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

Wowtab Technology [20, 21]

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

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

Flash Dose Technology [20, 21]

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 consists of self binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

Flashtab Technology [20, 21]

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.

Oraquick Technology [20, 21, 22]

The Oraquick fast dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its micro sphere technology, known as Micro Mask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste-masking Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

Each technology has a different mechanism, and each fast-dissolving/disintegrating dosage form varies regarding the following: [23]

* Mechanical strength of final product;
* Drug and dosage form stability;
* Mouth feel;
* Taste;
* Rate of dissolution of drug formulation in saliva;
* Swallow ability;
* Rate of absorption from the saliva solution; and
* Overall bioavailability.

Evaluation Of Blend

The prepared blend was evaluated by following tests.

Angle of repose

Bulk density

Tapped density

Carr’s index

Hauser’s ratio

Angle of repose

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipient blend was allowed to flow through the funnel Freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where h and r are the height and radius of the powder conc.

Bulk density

Apparent bulk density was determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight.

BD =Weight of the powder / Volume of the packing.

Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend.

The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2-second intervals. The tapping was continued until no further change in volume was noted.

TBD =Weight of the powder / volume of the tapped packing.

Compressibility Index

The Compressibility Index of the blends was determined by Carr's compressibility index.

Carr's compressibility index (%) = [(TBD-LBD) X 100] / TBD

A similar index has been defined by Hausner

Hauser's ratio = Tapped density/ Poured density

Hausner's ratio

1.25 – Poor flow =33% Carr

b) Compression

Mixed Blends were compressed by direct compression method using Cadmach single punch machine. Caput punches and die (8 mm.) were used in this study.

EVALUATION OF TABLETS

All the formulated Gliclazide fast dissolving tablets were subjected to the following quality control tests:

Weight variation

Friability

Hardness

Disintegration

Wetting Time

Water absorption Ratio

Taste / Mouth feel

In vitro Dissolution

Stability studies

Evaluation Parameter of MFDTs

Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated ..

Hardness:

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula

% Friability = [(W1-W2)100]/W1

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

Disintegration test:

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 oC, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Uniformity of dispersion:

Two tablets were kept in 100ml water and gently stirred for 2 minutes. The dispersion was passed through 22 meshes. The tablets were considered to pass the test if no residue remained on the screen.

Wetting Time:

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petridish containing 0.2% w/v solution (3ml). a tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color on the upper surface of the tablets was noted as the wetting time.

Water Absorption Ratio:

A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed. Water absorption ratio, R was determined by using following formula were given

R= 100 x Wa-Wb / Wb

Wb is the weight of tablet before water absorption

Wa is the weight of tablet after water absorption

Taste/ Mouth sensation

Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch was tested for the sensation by placing the tablet on the tongue. The healthy human volunteers were used for evaluation of mouth feel. Taste evaluation was done by a panel of 5 members using time intensity method. Sample equivalent to 40 mg i.e dose of drug was held in mouth for 10 secs. Taste were recorded instantly and then after 10 secs, 1, 2, 4 and 6 minutes. Volunteer's opinion for the taste were

rated by giving different score values i.e. .0 = good, 1 = tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful.

In vitro drug release studies

The Gliclazide fast dissolving tablets were subjected to in vitro drug release studies in pH 6.8 phosphate buffer for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in eight stage dissolution test apparatus (DISSO 2000, Lab India) using 900ml ml of dissolution medium (pH 6.8 phosphate buffer) maintained at 37±10C. The tablets were kept in the cylindrical basket and rotated at 100 rpm

5ml of the sample from the dissolution medium were withdrawn at each time interval (2, 3, 5, 10, 15&30 minutes) and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml with pH 6.8 Phosphate buffer. The absorbances of the sample were measured at λmax 227.2 nm using UV spectrophotometer.

In vitro dissolution kinetic studies

The drug released data were plotted and tested with zero order (Cumulative % drug released Vs time),First order (Log % Remained Vs time).The zero order release kinetics was shown in Figures

The First order release kinetics were shown in figures

The in vitro dissolution kinetic parameters,dissolution rate constants (K),correlation coefficient ® , the times (t50) for50% drug released (half life) and dissolution efficiency were calculated and presented in the tables of following chapters.From the slopes of linear plots, the dissolution rates were calculated.

First – order release kinetics log Q1 = logQo + k1t

2.303

The First order equation describes the release from systems where release rate is concentration dependent.Where Qo is the initial amount of the drug,t is in minutes and k1 describes the dissolution rate constant for first-order release kinetics.A plot of the logarithm of the percent drug remained against time will be linear if the release obeys first-order release kinetics.values of release rate constant k1 were obtained in each case from the slope of the log % drug remained versus time plots

Dissolution efficiency

DE is defined as the area under the dissolution curve upto the time “t” expressed as a percentage of the area of the trapezoid described by 100% dissolution in the same time.

DE = ∫td y.dt

Yidd.t

This has a range of values depending on the time interval choosen. For example , the index DE30 would relate to the dissolution of the drug from a particular formulation after 30 mins could only be compared with DE30 of other formulations.

One way ANOVA

One way analysis of variance (ANOVA) compares the means of three or more groups.The null hypothesis is that all column means are equal,and P value testing this null hypothesis.

The one way ANOVA test assumes that data are randomly sampled from larger populations (or at least are representative of those populations) , that each value was obtained independently of others,that the populations are scattered accordingly to a Gaussian distribution,and that the SD of the two populations are equal.

It shows intermediate calculations that laed to calculate F value.if the calculated value is less than tabulated value , it can be concluded that the data are unlikely to be sampled from populations with equal means.

Two way ANOVA

When it is believed that two independent factors might have an effect on the response variable of interest, it is possible to design the test so that an analysis of variance can be used to test for the effects of the two factors simultaneously. Such a test is called a Two-Factor analysis of variance. With this we can test two sets of hypothesis with the same data at the same time.

In this the data are classified according to two different criteria of factors. The procedure for analysis of variance is somewhat different than the one followed while dealing with problems of one-way ANOVA.(statistical methods – S.P.Gupta,34th edn,2005-pg no.-1019)

Similarity and Dis-similarity factor

Purpose of dissolution profile comparison:

For accepting product sameness under SUPAC-related changes.

To waive bioequivalence requirements for lower strengths of a dosage form.

To support waivers for other bioequivalence requirements.

Dissolution profiles may be considered similar by virtue of (1) overall profile similarity and (2) similarity at every dissolution sample time point. The dissolution profile comparison may be carried out using model independent or model dependent methods.

Model Independent Approach Using a Similarity Factor

A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles. The difference factor (f1) calculates the percent (%) difference between the two

curves at each time point and is a measurement of the relative error between the two curves:

where n is the number of time points, Rt is the dissolution value of the reference (prechange) batch at time t, and Tt is the dissolution value of the test (postchange) batch at time t.

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

A specific procedure to determine difference and similarity factors is as follows:

Determine the dissolution profile of two products (12 units each) of the test (postchange) and reference (prechange) products.

Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f1) and similarity factor (f2) using the above equations.

For curves to be considered similar, f1 values should be close to 0, and f2 values should be close to 100. Generally, f1 values up to 15 (0-15) and f2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test (postchange) and reference (prechange) products.

This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. As further suggestions for the general approach, the following recommendations should also be considered:

The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both the profiles should be the same (e.g., 15, 30, 45, 60 minutes). The reference batch used should be the most recently manufactured prechange product.

Only one measurement should be considered after 85% dissolution of both the products.

To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%.

The mean dissolution values for Rt can be derived either from (1) last t prechange (reference) batch or (2) last two or more consecutively manufactured prechange batches.(same above-pg-1006)

Stability studies

The best formulation of Gliclazide MFDTs containing (CPV + CCM in 75:25 ratio) were subjected to stability study by keeping them at 40oC/75% RH for 1 month to assess their stability with respect to their physical appearance and release characteristics. The physical characteristics like weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time, mouth feel & in vitro release profile were determined at interval of 15& 30 days.

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