



Review Article

FAST DISSOLVING TABLETS AS NOVEL DOSAGE FORM

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ABSTRACT

The main aim of this review is to emphasise mainly on the advantages of fast dissolving tablets over conventional tablets, techniques used to make FDDS and which technique is suitable for particular dosage form.

Keywords: Conventional tablets, FDDS, Dosage form, Novel drug delivery.

INTRODUCTION

Patients who may have difficulty swallowing tablets or liquids, traditional tablets and capsules administered with an 8-oz. (One glass) of water may be inconvenient or impractical for some patients. However, some patients, particularly paediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many paediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant in the form of a Caplet shaped Tablet. Recent trends in Pharmaceutical formulation development technology have presented viable dosage alternatives for example; an eight-year-old with allergies could use a more convenient dosage form than antihistamine syrup. A schizophrenic patient in the institutional setting can hide a conventional

tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker. Fast-dissolving tablets (FDTs) / orally disintegrating tablets (ODTs) are a perfect fit for all of these patients. Fast-dissolving drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. There are multiple fast-dissolving OTC and Rx products on the market worldwide, most of which have been launched in the past 3 to 4 years. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology.

DEFINITION

The Centre 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 seconds, when placed up on the tongue”. FDTs 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 oesophagus as the saliva passes down into the stomach.

In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Their growing importance was underlined recently when European Pharmacopoeia adopted the term “**Orodispersible Tablet**” as a tablet that to be placed in oral cavity where it disperses rapidly before swallowing.

Salient Features of Fast Dissolving Drug Delivery System:

1. Ease of administration for patients who are mentally ill, disabled and uncooperative.
2. Requires no water.
3. Quick disintegration and dissolution of the dosage form.
4. Overcomes unacceptable taste of the drugs.
5. Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.
6. Allows high drug loading.
7. Ability to provide advantages of liquid medication in the form of solid preparation. Adaptable and amenable to existing processing and packaging machinery.
8. Cost-effective.

SIGNIFICANCE OF ORAL DISINTEGRATING TABLETS

Oral Disintegrating Tablets offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

Accurate dosing -Being unit solid dosage forms, provide luxury of accurate dosing, easy Portability and

manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients.

Enhanced bioavailability -

Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and oesophagus.

Rapid action –

Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

Patient compliance -

No need of water to swallow the dosage form. Hence, it is convenient for patient who are travelling and do not have immediate access to water.

Ease of administration -

Convenient to administer specially for geriatric, paediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.

Obstruction free -

No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

Enhanced palatability -

Good mouths feel, especially for paediatric patients as taste masking technique is used to avoid the bitter taste of drug.

Simple packaging -

No specific packaging required. It can be packaged in push through blisters.

Business Avenue -

Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

Cost effective -

Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

CHARACTERISTICS OF FAST DISSOLVING DELIVERY SYSTEM

1. Ease of administration: Fast Dissolving Delivery Systems are easy to administer and handle hence, leads 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.

2. Taste of the medicament: As most drugs are unpalatable, mouth dissolving delivery systems usually contain the medicament in taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste bud and hence, masking of the drugs becomes critical to patient compliance.

3. Hygroscopicity: Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which called for special packaging.

4. Friability: In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging

5. 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 flavours can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavour. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

Conventional Techniques Used in the Preparation of Fast Dissolving Drug Delivery System

Various techniques used in preparation of fast dissolving tablets include;

Freeze-Drying or Lyophilisation:

Freeze drying is the process in which water is sublimed from the product after it is frozen.

This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here.

The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight

and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine.

Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability.

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

Tablet Molding:

Moulding process is of two types i.e. solvent method and heat method.

Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution.

The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophilisation technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

Spray drying:

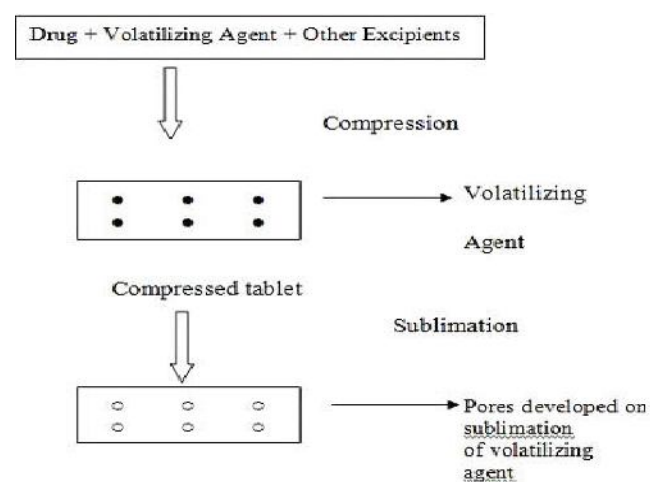
In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium

starch glycolate or croscarmellose or crospovidone are used as superdisintegrants.

Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Sublimation:

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane and benzene can be used as poring agents.



Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the

availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution.

The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel.

Mizumoto et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltitol) exhibit high mouldability but low dissolution rate.

Mass-Extrusion:

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 tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

Important Patented Technologies for Fast Dissolving Tablets:

1. Zydys Technology:

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 material designed to achieve a number of objectives. To impart

strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form 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 while 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.

2. Durasolv Technology:

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

3. Orasolv Technology:

CIMA labs have developed Orasolv Technology. 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.

4. Flash Dose Technology:

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.

5. Wow tab Technology:

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water".

In this process, combination of low mouldability saccharides and high mouldability dissolution rate saccharides is used to obtain a rapidly melting strong tablet. The active ingredient

is mixed with a low mouldability saccharide (e.g. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (e.g. Maltose, oligosaccharides) and compressed into tablet.

6. Flash tab Technology:

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation.

Drugs to be promising incorporate in FDTs

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient.

Analgesics and Anti-inflammatory Agents:

Aloxiaprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.

Anthelmintics:

Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Ivermectin, Mebendazole, Oxarnniquine, Oxfendazole, Praziquantel, Pyrantel Embonate, Thiabendazole.

Anti-Arrhythmic Agents:

Amiodarone, Disopyramide, Flecaïnide Acetate, Quinidine Sulphate.

Anti-Epileptics:

Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methyl phenobarbitone, Phensuximide, Phenytoin, Primidone, Valproic acid.

Anti-Arrhythmic Agents:

Amiodarone, Disopyramide, Flecaïnide Acetate, Quinidine Sulphate.

Anti-bacterial Agents:

Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Cloxacillin.

Anti-coagulants:

Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.

Anti-Depressants:

Amoxapine, Ciclazindol, Maprotiline, Mianserin, Nortriptyline, Trazodone, Trimipramine Maleate.

Anti-Epileptics:

Beclamide, Carbamazepine, Clonazepam, Ethoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid.

Anti-Fungal Agents:

Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Sulconazole Nitrate, Terbinafine, Terconazole, Tioconazole, Undecenoic Acid.

Anti-Gout Agents:

Allopurinol, Probenecid, Sulphinpyrazone.

Anti-Hypertensive Agents:

Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidil, Nicardipine, Nifedipine, Nimodipine,

Anti-Malarial:

Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate.

Anti-Migraine Agents:

Dihydroergotamine Mesylate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate, Sumatriptan Succinate.

Anti-Muscarinic Agents:

Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine Butyl Bromide, Hyoscyamine, Mepenzolate Bromide, Orphenadrine, Oxyphencylmine, Tropicamide.

Immunosuppressants:

Aminoglutethimide, Amsacrine, Azathioprine, Busulphan, Chlorambucil, Cyclosporine, Dacarbazine, Estramustine, Etoposide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitotane, Mitozantrone, Procarbazine, Tamoxifen Citrate, Testolactone.

Anti Protozoal Agents:

Benznidazole, Clioquinol, Decoquinol, Diiodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.

Anti-Thyroid Agents:

Carbimazole, Propylthiouracil.

Anxiolytic, Sedatives, Hypnotics and Neuroleptics:

Alprazolam, Amobarbitone, Barbitone, Bentazepam, Bromazepam, Bromperidol, Brotizolam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Clobazam, Clozapine, Diazepam, Droperidol, Ethinamate, Flunaison, Flunitrazepam, Flupromazine, Fluphenazine Decanoate, Flurazepam, Haloperidol, Lorazepam, Lormetazepam, Medazepam, Meprobamate, Methaqualone, Midazolam, Nitrazepam, Oxazepam, Pentobarbitone, Perphenazine Pimozide, Prochlorperazine, Suipiride, Temazepam, Thioridazine, Triazolam, Zopiclone.

Cardiac Inotropic Agents:

Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin.

Corticosteroids:

Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate, Desoxymethasone, Dexamethasone, Fludrocortisone Acetate, Flunisolide, Flucortolone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone.

Diuretics:

Acetazolamide, Amiloride, Bendroflumazide, Bumetanide, Chlorothiazide, Chlorthalidone, Ethacrynic Acid, Frusemide, Metolazone, Spironolactone, Triamterene.

Anti-Parkinsonian Agents:

Bromocriptine Mesylate, Lysuride Maleate.

Gastro-Intestinal Agents:

Bisacodyl, Cimetidine, Cisapride, Diphenoxylate, Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron, Ranitidine, Sulphasalazine.

Histamine H₁-Receptor Antagonists:

Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadine, Dimenhydrinate, Flunarizine, Loratadine, Meclozine, 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, Glyceryl Trinitrate, Isosorbide Dinitrate,

Isosorbide Mononitrate, Pentaerythritol Tetranitrate.

Nutritional Agents:

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

Opioid Analgesics:

Codeine, Dextropropoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine.

Oral Vaccines:

Vaccines designed to prevent or reduce the symptoms of diseases of which the following is a representative

Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, Aids, Measles, Lyme Disease, Travellers Diarrhoea, Hepatitis A, B And C, Otitis Media, Dengue Fever, Rabies, Para influenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhagic Fever, Argentina Haemorrhagic Fever, Caries, Chagas Disease, Urinary Tract Infection Caused By E.Coli, Pneumococcal Disease, Mumps, File:///H:/Gits Mdt\Fast Dissolving Tablet The Future of Compaction And Chikungunya.

Proteins, Peptides and Recombinant Drugs:

Insulin (Hexameric/Dimeric/Monomeric Forms), Glucagon, Growth Hormone (Somatotropin), Polypeptides or Their Derivatives, (Preferably With A Molecular Weight from 1000 To300,000), Calcitonins And Synthetic Modifications Thereof, Enkephalins, Interferons (Especially Alpha-2 Interferons For Treatment Of Common Colds).

Sex Hormones:

Clomiphene Citrate, Danazol, Ethinyloestradiol, Medroxyprogesterone Acetate, Mestranol, Methyltestosterone, Norethisterone, Norgestrel, Oestradiol, Conjugated Oestrogens, Progesterone, Stanozolol, Stibioestrol, Testosterone, Tibolone.

Stimulants:

Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, pemoline.

EXCIPIENTS USED IN FAST DISSOLVING TABLETS:

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-dissolving 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

Contributes functions of a diluents, 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 hydrolysate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition. The excipients could be ranked in descending order in terms of their brittleness:

microcrystalline cellulose > spray-dried lactose > beta lactose > alpha lactose > alpha lactose monohydrate > dicalciumphosphatedihydrate.

The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouth feel. Mizumito et al classified sugar-based excipients into two types on the basis of molding and dissolution rate:

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate

Type 2 saccharides (maltose and maltitol) exhibit high mouldability but low dissolution rate.

Properties of superdisintegrants:

1. Croscarmellose sodium: High swelling capacity, effective at low concentration. used in upto5% concentration. Insoluble in water, rapidly disperse in water and swells but does not gel even after long exposure.

2. Crospovidone: Greatest swelling and surface area as compare to other disintegrants used in 1-3% concentration. Available in micronized form.

3. Sodium starch glycolate: Absorb water rapidly; result in swelling upto 6%.

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-dissolving tablet formulation, including alkyl sulphates, 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 excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth 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.

SUPERDISINTEGRANTS:

Disintegrants are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of dosage form in dissolution fluids. An oral solid dosage form should ideally disperse into the primary particles from which it was prepared. Superdisintegrants are generally used at a low concentration, typically 1-10% by weight relative to

total weight of dosage unit. Generally employed superdisintegrants are crosscarmellose sodium (Ac-Di-Sol), Crospovidone (CP), sodium starch glycolate (SSG) etc. which represent example of crosslinked cellulose, crosslinked polymer and crosslinked starch respectively.

Selection of appropriate formulation excipients and manufacturing technology is necessary for obtaining the optimized design features of orally disintegrating dosage forms. Ideally, superdisintegrants should cause the tablet to disrupt, not only into the granules from which it was compressed but also into powder particles from which the granules were prepared.

Selection of superdisintegrants:

Although superdisintegrants primarily affect the rate of disintegration, but when used at high levels they can also affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting an appropriate superdisintegrants for a particular formulation should:

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

Mechanism of action of disintegrant:

Various mechanisms proposed in this concern include water wicking, swelling, deformation recovery, repulsion and heat of wetting. It seems likely that no single mechanism can explain the complex behaviour of the disintegrants. However, each of these proposed mechanisms provides some understanding of different aspects of disintegrant action.

Water wicking:

The ability of disintegrant to draw water into the porous network of tablet is essential for effective disintegration. On keeping the tablet into suitable aqueous medium, the medium enters into tablet and replaces the air adsorbed on the particles which weakens the intermolecular bonds and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipients and on tableting conditions. Unlike swelling, which is mainly a measure of volume expansion with accompanying force

generation, water wicking is not necessarily accompanied by a volume increase. The ability of a system to draw water can be summarized by Washburn's equation:

$$L^2 = (\gamma \cos\theta / 2\eta) \times \pi t$$

The Washburn equation is too simplistic to apply to a dynamic tablet-disintegration process, but it does show that any change in the surface tension (γ), pore size (r), solid-liquid contact angle (θ) or liquid viscosity (η) could change the water wicking efficiency. L is the length of water penetration in the capillary and t is the time. This process is also considered as capillary action method.

Swelling:

Although water penetration is a necessary first step for disintegration, swelling is probably the most widely accepted mechanism of action for tablet disintegrants. For swelling to be effective as a mechanism of disintegration, there must be a superstructure against which disintegrant swells. Figure below represents the disintegration of tablet by wicking and swelling. Swelling of the disintegrant against the matrix leads to development of a swelling force. A large internal porosity in the dosage form in which much of the swelling can be accommodated reduces the effectiveness of the disintegrant. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slowed down.

Heat of wetting:

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

Due to release of gases:

Carbon dioxide gets released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during preparation of the tablets. The effervescent

blend is either added immediately prior to compression or can be added into two separate fractions of formulation.

Generation of pressure within the tablet:

This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet.

As Particle repulsive forces:

This is another mechanism of disintegration that attempts to explain the swelling of tablet made with non-swellable disintegrants. Guyot-Hermann proposed a particle-particle repulsion theory to explain the observation that particles which do not swell extensively such as starch, could still disintegrate tablets. According to this theory, water penetrates into tablet through hydrophilic pores and a continuous starch network is created that can convey water from one particle to the next, imparting a significant hydrostatic pressure. The water then penetrates between starch grains because of its affinity for starch surfaces, thereby breaking hydrogen bonds and other forces holding the tablet together. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

Deformation recovery:

Deformation recovery theory implies that the shape of disintegrant particles is distorted during compression and the particles return to their precompression shape upon wetting, thereby causing the tablet to break apart. Such a phenomenon may be an important aspect of the mechanism of action of disintegrants such as Crosspovidone and starch that exhibit little or no swelling.

By enzymatic reactions:

Enzymes present in the body also act as disintegrants. These enzymes dearth the binding action of binder and helps in disintegration.

Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration.

Application of Various Commercially Used Combinations of Modified Cellulose/Starch Used in ODTs

Superdisintegrant and Disintegrants				Applications		
Brand Name	Common Name	Classification	Functional Category	Properties	EMC at 25°C/ 90%RH	Typical Uses
CL-Kollidon	Crospovidone	Polyvinyl-pyrrolidone	Tablet super disintegrant	Swelling (18% in 10s), (45% in 20s)	62%	Disintegrant (Dry and Wet granulation)
Ac-DiSol	Croscarmellose Sodium	Cellulose, carboxy-methyl ether, sodium salt cross linked	Tablet and capsule disintegrant	Wicking and swelling (12% in 10s), (23% in 20s)	88%	Disintegrant for capsules, tablets and granules
Explotab	Sodium starch Glycolate	Sodium carboxymethyl Starch	Tablet and capsule super disintegrant	Swelling capacity (300 times)	-----	Disintegrant (Dry and Wet granulation)
Explotab V17	Sodium starch Glycolate	(Cross linked substituted Carboxy-methyl ether) sodium carboxymethyl starch	Super Disintegrant	More swelling than Explotab		Disintegration & dissolution aid. Not for use in wet Granulation
Explotab CLV	Sodium starch Glycolate	(Cross linked low substituted Carboxy-methyl ether) Sodium carboxymethyl starch	Super disintegrant	Swelling		Use in wet granulation and high shear equipment
L-HPC	Hydroxypropyl cellulose(low substituted)	Cellulose, 2-hydroxypropyl Ether	Tablet and capsule super disintegrant	Swelling (13% in 10s), (50% in 20s)	37%	Disintegrant and Binder in wet granulation
Starch 1500	Starch, Pre-gelatinized	Pregelatinized Starch	Diluent, binder and disintegrant	Hygroscopic	22%	Binder/diluent & disintegrant
Avicel	Microcrystalline Cellulose	Cellulose	Tablet & capsule diluents, Tablet disintegrant	Hygroscopic, swelling- (12% in 10s), (18% in 20s)	18%	Binder/diluent, lubricant and disintegrant

TASTE MASKING TECHNOLOGIES

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers. Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g., Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and

complete dissolution in a short period. Fine granules of drug and disintegrant (e.g. low substituted Hydroxypropyl cellulose) when coated with a water insoluble polymer (e.g. ethyl cellulose) masked the bitter taste of sparfloxacin. The addition of low substituted Hydroxypropyl cellulose as disintegrant to the drug in cores resulted in increased dissolution rate and bioavailability of sparfloxacin compared to its conventional tablets.

Ozer and Hincal reported a simple coacervation method

using gelatin, and anhydrous sodium sulphate as coacervating agent for taste making of beclamide. Beclamide is an anti-epileptic drug with unpleasant taste. It is microencapsulated into gelatin, with sodium sulphate as coacervating agent, and glutaraldehyde as hardening agent. The microcapsules after formation are dehydrated using alcohol. The core: wall substance ratio was 1:1, and the taste could be successfully masked.

Table. 1: Taste masking using flavours and sweeteners

SL No	Drug(s)	Taste masking agent(s)
1.	Aspirin	Sodium phenolate
2.	Chlorpheniramine, Phenyl propanolamine	Sod. bicarbonate, citric acid, orange/cream flavour
3.	Famotidine	Sod. bicarbonate, citric acid, lemon flavour
4.	Ibuprofen	Sod. citrate dihydrate, sod. saccharin, refined sugar
5.	Theophylline	D-sorbitol, sodium saccharin, sodium glutamate, and vanilla essence
6.	Acetaminophen	Sod. bicarbonate, citric acid, cherry flavour
7.	Caffeine	Starch, lactose, and mannitol

Table. 2: Taste masking using lipophilic vehicles

S. No	Drug(s)	Taste masking agent(s)
1.	Isoprothiolane	Hydrogenated oil and HPMC
2.	Acetaminophen	Molten stearyl stearate
3.	Talampicillin HCl	Magnesium aluminum silicate & soyabean lecithin
4.	Clarithromycin	Glyceryl monostearate and AMCE
5.	Indeloxazine HC	Hydrogenated oil and surfactants

HPMC=Hydroxypropyl methyl cellulose; AMCE=Aminoalkyl methacrylate copolymer E

Table. 3: Taste masking using polymer coating

S.No	Drug(s)	Polymer(s) used
1	Pinaverium bromide	Cellulose or shellac
2	Ibuprofen	Methacrylic acid copolymer (Eudragit)
3	Amoxycillin trihydrate	MCC, L-HPC
4	Clarithromycin	Carbopol, PVP
5	Roxithromycin	PEG, Eudragit L 100–55
6	Cefuroxime axetil	Eudragit L-55 and RL
7	Pirenzepine & Oxybutynin	Eudragit E-100, MCC, HPC
8	Levofloxacin	Eudragit E100, cellulose acetate

HPMC= Hydroxypropyl methyl cellulose; HEC= Hydroxyethyl cellulose; HPC=Hydroxypropyl cellulose; L-HPC= Low substituted hydroxypropyl cellulose; CMC= Carboxy methyl cellulose; PVP= Polyvinyl pyrrolidone; EC=Ethyl cellulose; MCC= Microcrystalline cellulose; PEG= Polyethylene glycol; TiO₂=Titanium dioxide.

Table. 4: List of drugs and taste masking ion exchange resins

S. No	Drug(s)	Resin/complexing agent
1	Carbetapentane citrate	Cyclodextrin
2	Ibuprofen	Hydroxypropyl b-cyclodextrin
3	Diphenhydramine HCl	Indion CRP 244, indion CRP 254
4	Bufloxedil	Amberlite IRP 69
5	Orbifloxacin	Amberlite IRP 69
6	Orbifloxacin	Amberlite IRP 69

A novel technique for taste masking of macrolides (e.g. erythromycin and clarithromycin) is reported by Yajima.

Monoglycerides having a low melting point which can form good elaborate film, and easily soluble in intestine, and polymers which are insoluble in the mouth (pH 5-8), but are freely soluble in stomach (pH 1-4), are selected for taste masking of drugs with unpleasant taste. The polymer is dissolved or dispersed in monoglyceride, and the drug is granulated with above mixture and the resultant granules are cooled.

Traditional taste masking techniques in oral pharmaceuticals:

Taste masking using flavours and sweeteners: Artificial sweeteners and flavours are generally being used along with other taste-masking techniques to improve the efficiency of these techniques in dentifrices, mouthwashes and cough drops. The examples are given in table no.1

Taste masking using Lipophilic Vehicles: - It is the property of oils, surfactants, polyalcohol and lipids to increase the viscosity in the mouth and to coat the taste buds and therefore they are potential taste masking agents. Formulations with a large excess of lecithin or lecithin like substances are claimed to control bitter taste in pharmaceuticals. Examples are given in table no.2

Taste masking by Coating with Hydrophilic Vehicles: Carbohydrates can be used as a coating material to mask the taste of orally administered drugs. Various forms of proteins have been used extensively for taste masking. Some examples are given in Table no.3

Taste masking by Ion-Exchange Resins (IERS):- To stabilize the sensitive components, to sustain the drug release, to disintegrate tablets, and to mask taste, ion-exchange resins are used in formulations. Some examples of drugs and taste masking agents and ion exchange resins are given in Table no.4.

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)-excipients 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:

$$\tan \alpha = h/r$$

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.

Evaluation of Fast dissolving tablets

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation is given by the formula.

%weight variation

$$= \frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \times 100$$

Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm².

Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Prewighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{final}}$$

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = rY\cos\theta/(4\eta l)$$

Where l is the length of penetration, r is the capillary radius, γ is the surface tension, η is the liquid viscosity, t is the time, and θ is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

In vitro drug release -

Release of the drug in vitro, was determined by estimating the dissolution profile, USP 2 Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, phosphate buffer (PH 6.8) (900 ml) was used as a dissolution medium.

Mechanical Strength -

Tablets should possess adequate strength to withstand mechanical shocks of handling in Manufacturing, packaging

and shipping. Crushing strength and friability are two important parameters to evaluate a tablet for its mechanical strength.

Crushing Strength -

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported.

Friability testing

The crushing test may not be the best measure of potential behaviour during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measure in "Electro lab friabilator". Ten preweighed tablets were rotated at 25 rpm for 4 min, the tablets were then re weighed and the percentage of weight loss was calculated.

Rapidly Disintegrating Property

To evaluate the tablets for their rapid disintegration properties, following tests were carried out.

Modified disintegration test

The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for ODT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the centre of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

Disintegration in oral cavity

The time required for complete disintegration of tablets in oral cavity was obtained from six healthy volunteers, who were given tablets from the optimum formulation Water absorption Ratio A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R , was determined using following equation,

$$R = 10(w_a/w_b)$$

Where, w_b = weight of tablet before water absorption & w_a is weight of tablet after water absorption.

CONCLUSION

The fundamental principle used in the development of the fast-dissolving tablet is to maximize its pore structure. Researchers have evaluated spray dried materials and plastic materials for development of such tablets. Vacuum-drying and freeze-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum-drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets.

It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. The basic approach followed by all the currently available technologies engaged in the formulation of Fast dissolving tablets is to maximize the porous structure of the tablet matrix and incorporate super disintegrating agents in optimum concentration so as to achieve rapid disintegration and instantaneous dissolution of the tablet along with good taste masking properties and excellent mechanical strength. The availability of the various technologies and manifold advantages of Fast dissolving tablets will surely increase its popularity in the near future. However, geriatric and paediatric 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 paediatric 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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