



A Review on Fast Dissolving Drug Delivery Systems- A Pioneering Drug Delivery Technology

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ABSTRACT

The Fast Dissolving Drug Delivery Systems was an advancement that came into existence in the early 1970's and combat over the use of the tablets, syrups, capsules which are the other oral drug delivery systems. Fast Dissolving Drug Delivery Systems serves as a major benefit over the conventional dosage forms since the drug gets rapidly disintegrated & dissolves in the saliva without the use of water. In spite of the downside i.e., lack of immediate onset of action; these oral dosage forms have beneficial purposes such as self medication, increased compliance, ease of manufacturing and lack of pain. Hence Fast Disintegrating Tablet (FDT) technology has been gaining significance now-a-days with wide variety of drugs serving many purposes. Fast Disintegrating Tablets (FDT) has ever increased their demand in the last decade since they disintegrate in saliva in less than 60 seconds.

Keywords: Fast Dissolving Drug delivery systems, patented technologies, conventional technologies, evaluation of FDTs.

INTRODUCTION

The concept of FDTs came into view with an objective of increased patient compliance. As the cost for developing a generic molecule is too high, the research is being done on the new dosage forms for having better compliance as compared to the different dosage forms of which the oral route serves to make an attribution. Some patients, particularly pediatric and geriatric patients¹, have difficulty swallowing or chewing solid dosage forms. 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. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing².

The main proposal of the present review is to study the practicability of fast dissolving drug delivery and illustrate briefly the ideal properties, advantages and limitations, conventional and patented technologies, available marketed formulations in FDTs and evaluation methods.

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."³FDTs disintegrate and/or dissolve instantaneously in the saliva without the use of 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 disintegrate⁴. When placed on tongue, this tablet disintegrates rapidly, 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.

Ideal Properties of Fast Dissolving Tablets:

1. Require no water for oral administration.
2. Should be harder and less friable.
3. Have an acceptable taste masking property.
4. Leave minimal or no residue in mouth after administration
5. Exhibit low sensitivity to environmental conditions (temperature and humidity).
6. Cost-effective production techniques

Advantages of Fast Dissolving Tablets:

1. Ease of administration to patients who cannot swallow like the bed-ridden, stroke victims and patients who refuse to swallow like geriatrics, pediatrics and psychiatrics.
2. Good mouth feel property
3. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.

Limitations of Mouth Dissolving Tablets⁵:

1. The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2. FDT requires special packaging for proper stabilization and safety of stable product.

Ideal Drug Candidates of Fast Dissolving Tablets

1. The dose must be lower than 20 mg.
2. The drug should be partially unionized at oral pH.
3. Drug should permeate through the oral mucosal tissue.⁶

Potential candidates for fast dissolving tablets

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, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, 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, Disopyramide, Flecainide Acetate, Quinidine Sulphate

Anti-bacterial Agents:

Benethamine, Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Cloxacillin, Demeclocycline, Doxycycline, Erythromycin, Ethionamide, Imipenem, Nalidixic Acid, Nitrofurantoin, Rifampicin, Spiramycin, Sulphabenzamide, Sulphadoxine, Sulphamerazine, Sulphacetamide, Sulphadiazine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine,

Anti-coagulants:

Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.

Anti-Depressants:

Amoxapine, Ciclazindol, Maprotiline, Mianserin, Nortriptyline, Trazodone, Trimipramine Maleate, Acetohexamide, Chlorpropamide, Glibenclamide, Glucilazide, Glipizide, Tolazamide, Tolbutamide.

Anti-Epileptics:

Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacetamide, 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, Diltiazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidil, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.

Anti-Malarials:

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, Oxyphencylamine, Tropicamide.

Anti-Neoplastic Agents and Immunosuppressants:

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

Anti -Protozoal Agents:

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

Anti-Thyroid Agents:

Carbimazole, Propylthiouracil.

Anxiolytic, Sedatives, Hypnotics and Neuroleptics:

Alprazolam, Amyobarbitone, Barbitone, Bentazepam, Bromazepam, Bromperidol, Brotizolam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Clobazam, Clotiazepam, Clozapine, Diazepam, Droperidol, Ethinamate, Flunarisone, Flunitrazepam, Fluopromazine, Flupenuixol Decanoate, 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, Fluticasone Propionate, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone.

Diuretics:

Acetazolamide, Amiloride, Bendrofluazide, 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 H 1-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, Glycerol Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate.

Nutritional Agents:

Betacarotene, Vitamin A, Vitamin B 2, Vitamin D, Vitamin E, Vitamin K.

Opioid Analgesics:

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

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 To 300,000), Calcitonin And Synthetic Modifications Thereof, Enkephalins, Interferons (Especially Alpha-2 Interferon For Treatment Of Common Cold).

Sex Hormones:

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

Stimulants:

Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol, pemoline.

There are no particular limitations on the amount of these drugs to be mixed as long as it is the usual effective treatment amount. It should be around 50 weight/weight % or below of the entire tablet, and is preferably 20 weight/weight % or below.

Selection of Excipients^{7,8}

Excipients balance the properties of the active ingredients in fast-melting tablets. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy.

Bulk Agents:

Bulk agents are significant in the formulation of fast-dissolving tablets. The material contribute functions of a diluent, filler and cost reducer. Bulk 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.

The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart tastemasking property. Mizumoto *et al*, classified sugar-based excipients 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.

Emulsifying agents:

These 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 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 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.

Flavors and Sweeteners:

Flavors and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients aids in overcoming bitterness and disagreeable tastes of some active ingredients. Both natural and synthetic flavors can be used to improve the organoleptic characteristics 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.

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. Superdisintegrants are generally used at a low concentration, typically 1-10% by weight relative to total weight of dosage unit. Generally employed superdisintegrants are croscarmellose sodium (Ac-Di-Sol), Crosspovidone (CP), sodium starch glycolate (SSG). 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.

Table1: Properties of Modified Starches/Celluloses Used in FDTs

| S.No. | Superdisintegrant | Properties |
|-------|------------------------|---|
| 1. | Croscarmellose sodium | High swelling capacity, effective at low concentration (0.5-2.0%); can be used up to 5%. |
| 2. | Crospovidone | Completely insoluble in water. 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 disintegrants. Effective concentration (1-3%). Available in micronized grades if needed for improving state of dispersion in the powder blend. |
| 3. | Sodiumstarch glycolate | Absorbs water rapidly, resulting in swelling up to 6%. High concentration causes gelling and loss of disintegration |

Techniques Employed In The Formulation Of Fast Dissolving Tablets

Many techniques have been reported for the formulation of Fast dissolving tablets or Orodispersible tablets

I. Conventional Technologies

1. Freeze drying / lyophilization 2. Tablet Moulding 3. Spray drying 4. Sublimation
5. Direct compression 6. Melt granulation 7. Mass extrusion 8. Cotton Candy process

1. FreezeDrying / lyophilisation:

The tablets prepared by freeze-drying or lyophilization are very porous in nature and disintegrate or dissolve quickly when come in contact with saliva. In this process, water is sublimated from the product after freezing. 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. First of all, the material is frozen to bring it below its eutectic point. Then primary drying is done to decrease the moisture to about 4% w/w of dry product. Lastly, secondary drying is made to reduce the bound moisture to the required volume. However the use of freeze-drying is restricted due to high cost of equipment and processing. A major limitation of the final dosage form comprises lack of physical resistance in standard blister packs.

2. Tablet Moulding:

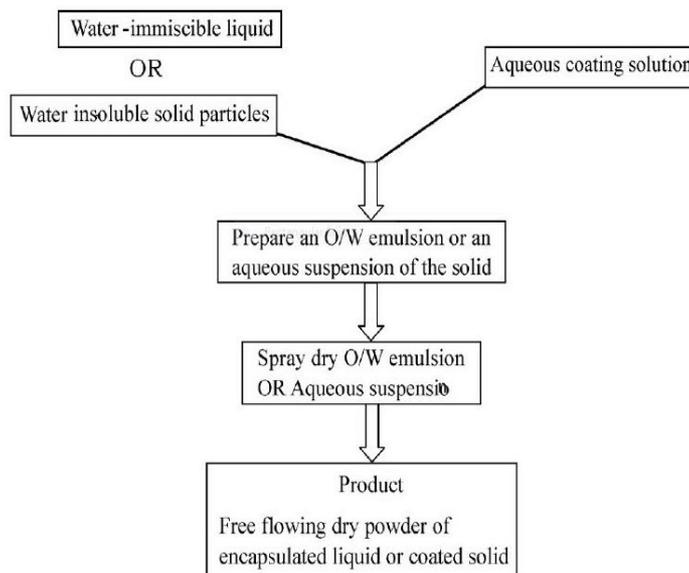
Moulding process is of two types i.e. solvent method and heat method. Solvent method involves damping the powder blend using an alcoholic solvent and later on compressing at low pressure in molded plates to form a wet mass (compression moulding). The solvent is then removed by air-drying. The tablets prepared by this technique are less compact than compressed tablets and possess a porous structure that accelerates the dissolution. The heat moulding 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 to be notified and hence binding agents are mixed to give strength. Taste masking is an additional trouble in 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 lyophilization method, tablets formed by the molding technique are easier to upgrade for industrial manufacture.

3. Spray Drying:

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and/ or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution.

Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

Figure 1: Flowchart for coating liquid and solid particles using spray-dry process



4. Sublimation:

Inert solid ingredients (ex. urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. The tablets dissolve in less than 20 seconds and exhibit sufficient mechanical strength. The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Hence to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe, Knitsch et al., and Roser and Blair, inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane) were compressed along with other excipients into a table⁹. The volatile material was then removed by sublimation, leaving behind a porous matrix.

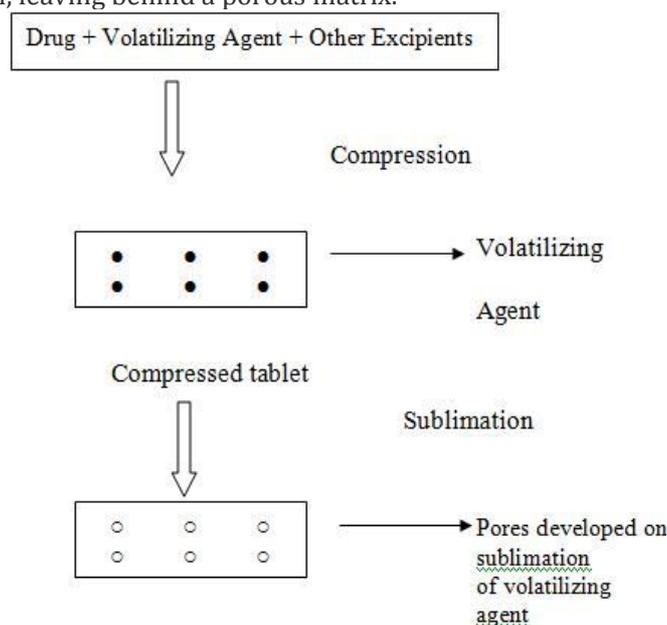


Figure 2: Schematic Diagram of Sublimation Technique for Preparation of FDT

5. Direct Compression:

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. The disintegration and solubilization of directly compressed tablets depends on single or combined action of disintegrants, water soluble excipients and effervescent agents used. Breakage of tablet edges during handling and tablet crack during the opening of blister alveolus, all result from insufficient physical resistance. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can promote improved dissolution or disintegration properties. But the main problem of using effervescent excipients is that they are highly hygroscopic in nature.

7. Melt Granulation:

Melt granulation technique is a process by which the pharmaceutical powders are capably agglomerated by a meltable binder. The benefit of this technique compared to a conventional granulation is that no water or organic solvents is required. Since there is no drying step, the process is less time consuming and requires less energy than wet granulation. It is a technique useful to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.¹⁰

8. Mass extrusion:

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and consequent removal 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 achieving taste masking.

9. Cotton candy process:

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

II. Patented Technologies:

i.) Zydis (R.P. Scherer, Inc.) ii.) Wowtab (Yamanouchi Pharma Technologies, Inc.) iii.) OraSolv (Cima Labs, Inc.) iv.) DuraSolv (Cima Labs, Inc.) v.) FlashDose (Fuisz Technologies, Ltd.) vi.) Flashtab (Prographarm Group) vii.) OraQuick (KV Pharmaceutical Co., Inc.) viii.) Quick -Dis Technology (Lavipharm Laboratories Inc.) ix.) Zipllets/Advatab, (Passano con Barnago, Italy) x.) Lyoc technology (PHARMALYCO) xi.) Pharmaburst technology (SPI Pharma, New Castle) xii.) Frosta technology (Akina) xiii.) Nanocrystal Technology (Elan, King of Prussia) xiv.) Quick solv (Janssen Pharmaceuticals).

i.) Zydis Technology:

Scherer has patented the Zydis 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. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. In addition, it utilizes microencapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter tasting drug.

ii.) Wowtab Technology

The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given "With Out Water". It is recently been introduced into the U.S. The Wowtab technology makes use of sugar and sugar-like (e.g., mannitol) excipients. This process is a blend of low mouldability saccharides (rapid dissolution) and high mouldability saccharides (good binding property). The two different types of saccharides are mixed to attain a tablet formulation with ample hardness and fast dissolution rate. Due to its significant hardness, the Wowtab formulation is slightly more stable to the environment than the Zydis or OraSolv.

iii.) OraSolv Technology

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. 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. The limitation associated is that the tablets produced are soft and friable. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing¹¹.

iv.) Durasolv Technology

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation developed in a similar fashion as that of the OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials. The key ingredients in this formulation are filler and lubricant. The particle size of the filler is preferably between about 20 and 65 µm. This method can produce tablets by using the direct compression method, conventional tableting methodologies and conventional package equipment. Thus, the production cost is significantly reduced.

v.) Flash Dose Technology:

Flash dose technology has been patented by Fuisz Technologies Ltd. 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.

vi.) Flashtab Technology:

Prographarm laboratories has patented the Flashtab technology. This technology engages in the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals/micro-granules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tablet technology, and the tablets produced are accounted to have good mechanical strength and disintegration time is less than 60 seconds¹².

vii.) Oraquick Technology

The OraQuick fast-dissolving/disintegrating tablet formulation employs a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as MicroMask, has better taste masking property. The taste masking process does not make use of any solvents and therefore leads to faster and more efficient production. OraQuick is appropriate for heat-sensitive drugs since utilizes lower heat for the production than the competing fast dissolving technologies.

viii.) Quick -Dis Technology

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick-Dis™, is Lavipharm's proprietary patented technology¹² and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.

ix.) Ziplets/Advatab

This technology is patented by Passano con Barnago, Italy. It employs water-insoluble ingredient merged with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force.

x.) Lyoc

Lyoc technology is patented by PHARMALYCO. Lyoc utilizes a freeze drying process but it differs from Zydis in that the product is frozen on the freeze dryer shelves. In order to prevent homogeneity by sedimentation during this process, these formulations also require a large proportion of undissolved inert filler such as mannitol, to increase the viscosity of the in process suspension. The high proportion of filler used reduces the potential porosity of the dried dosage form and hence results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations¹⁴.

xi.) Pharmaburst Technology

Pharmaburst technology is being patented by SPI pharma. The tablet manufactured by this process involves a dry blend of a drug, flavors, and lubricant then followed by compression into tablets which then dissolve within 30-40 seconds.

xii.) Frosta technology:

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

xiii.) **Nanocrystal Technology**

This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous ¹⁴.

xiv.) **Quicksolv Technology**

Quicksolv (Janssen Pharmaceutica, Beese,Belgium). In the Quicksolv formulation,the matrix compositions are dissolved in the solvent (usually water), and then this solution is frozen. At the temperature the first solvent will remain in the solid form, and then the frozen solution contacts the second solvent which is usually, ethanol, menthol, or acetone. Thus, the first solvent is removed after a few hours of contacting the second solvent to result in a usable matrix¹³. The final product disintegrates almost instantly.

Table 2 : Commercially available Patented Fast dissolving Technologies

| Patented Technology | Patent Holder | Technology Basis | Active Ingredients | Available Products |
|---------------------|--------------------------------------|-------------------------|-------------------------|---------------------------------------|
| Zydus | R.P.Scherer,Inc [Cardinal Health] | Freeze-drying | Loratidine | Claritin®Reditab |
| | | | Fanotidine | Pepcid®ODT |
| | | | Ondansetron | Zofran®ODT |
| | | | Selegiline | Zelapar™ |
| | | | Rizatritpan benzoate | Maxalt-®MLT |
| Lyoc | Farmayoc | Freeze-drying | Phloroglucinol hydrate | Spasfon lyoc |
| QuickSolv | Janssen pharmaceuticals | Freeze-drying | Cisapride monohydrate | Propulsid Quicksolv |
| Orasolv | Cima Labs Inc, | Direct compression | Mirtazapine | Remeron®SolTab |
| | | | Acetaminophen | Tempra Quicklets TempraFirs Tablet |
| Flash Dose | Biovail(Fuisz Technology, Ltd) | Cotton Candy Process | Tramadol HCl | Relivia Flashdose® |
| | | | Fluoxetine | FluoxetineODT |
| | | | Zolpidem Tertrate | Zolpidem ODT |
| Durasolv | Cima Labs Inc, | Direct compression | Zolmitriptane | Zolmig®ZMT |
| | | | Hyoscyamine Sulfate | Nulev® |
| | | | Baclofen | Kemstro™ |
| Flashtab | Prographarm laboratories | Direct compression | Ibuprofen | Nurofen®Flash Tab |
| Wowtab | Yamanouchi Pharma Tech,Inc | Direct compression | Famotidine | Gaster D |
| | | | Ramosetoron HCl | Nasea OD |
| | | | Diphenhydramine Citrate | Benadryl®Fastmelt |
| Oraquick | KV Pharm.Co.Inc. | Micromask taste masking | Hyoscyamine sulfate | Hyoscyamine sulphate ODT |
| Advatab | Eurand International, Dayton OH | Direct compression | Cetirizine | AdvaTab Cetirizine |
| | | | Paracetamol | AdvaTab Paracetamol |
| Ziplets | Eurand International, Dayton OH | Direct compression | Ibuprofen | Cibalginadue Fast |

Evaluation of Fast Dissolving Tablets:

1. Weight variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table 3.

Table 3: Limits for the weight variation of tablets:

| Average weight of tablet | % deviation |
|--------------------------------------|-------------|
| 80mg or less | ±10 |
| More than 80 mg but less than 250 mg | ±7.5 |
| 250mg or more | ±5 |

2. Tensile Strength

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using equation I:

$$\text{Eq. I. } T = 2F / \pi dt$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively. Though, this is a widely used and accepted method for hardness testing, it is not applicable to very delicate tablets prepared by lyophilization technique. Flashdose tablets prepared by cotton candy process are also poor candidates for this test¹⁵. This test is best suited for tablets prepared by direct compression and moulding methods. However, the tensile strength of these tablets is always kept low which needs to be compromised to keep the disintegration time as minimum as possible.

3. Friability

The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for FDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is again not applicable for lyophilized and flashdose tablets, but is always recommended for tablets prepared by direct compression and moulding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

4. Moisture Uptake Study

MDTs usually contain high concentration of hydrophilic excipients with the minimum possible hardness which together contribute to their increased susceptibility to moisture uptake hence special attention is required during the storage and packaging of these dosage forms. Therefore, moisture uptake studies are strongly recommended for FDTs. The test can be carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37 °C for 24 hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccator for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded. The use of appropriate quantity of desiccant in HDPE bottle packs with minimum head space is highly recommended to ensure stability of the product during its shelf life.

5. Tablet Porosity

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration. This instrument is based on the capillary rise phenomenon wherein an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure difference across the interface is given by the Washburn equation II, where the pressure drop is inversely related to the pore size (perpendicular radius).

$$\text{Eq. II. } \Delta P = -(2\gamma/r) \cos \theta$$

Where γ is the surface tension of the liquid, r is the perpendicular radius and θ is the angle of contact between the liquid and the capillary walls. Pore radius is calculated from eq II using experimental data obtained in the form of P. In this test, the contact angle between mercury and the tablet is kept at 140°C and the surface tension at the interface of mercury and the tablet is 0.486 N/m. Pore sizes in the range of 0.06–360 μm , can be efficiently measured by this technique. Otherwise, the tablet porosity (ϵ) can also be calculated using equation III:

$$\text{Eq. III. } \epsilon = 1 - m / (\rho t V)$$

Where ρt , is the true density, and m and V are the weight and volume of the tablet, respectively ³¹.

6. Wetting Time and Water Absorption Ratio

A study on wetting time and water absorption ratio reported the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R, was determined according to equation IV:

$$\text{Eq. IV. } R = 100 (W_a - W_b) / W_b$$

Where W_b and W_a are the weights of tablet before and after water absorption, respectively.

7. In vivo disintegration time

The time for disintegration of ODTs is generally <1 minute and actual disintegration time that patient can experience ranges from 5 to 30 seconds. 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 test for ODT should mimic disintegration in mouth within salivary contents. Various disintegration methods developed are discussed

Table 4: Invitro disintegration methods for FDTs:

| In vitro disintegration method | Characteristic features | Critical parameters |
|--------------------------------|---|---|
| Modified USP apparatus II | One litre cylindrical vessel, paddle as stirring element, basket sinker with FDT was placed in middle of vessel and hang by a hook to the lid of vessel with distance of 6-8.5 cm | Medium 900ml , temperature 37°C , paddle 100 rpm |
| Rotary shaft method | Stainless steel wire gauge on which FDT is placed and slightly merged in medium. Rotary shaft employed to provide mechanical stress and rotation. | Rotational speed, mechanical stress |
| Sieve method | Glass cylinder with 10 mesh sieve device is placed in shaking water bath operated at 150 rpm | Medium 1ml , temperature 37°C , shaking speed of water bath |
| Texture analyser | Cylindrical flat pro the button which is adhered by FDT , which was attached to load cell with very thin layer of glue. FDT submerged in medium present in beaker/ Petri dish and compressed. Distance travelled by pro into tablet is measure of disintegration time. | Force of compression , medium 0.4 ml water. Room temperature, measure beginning and ending of disintegration time |
| Charge couple device method | Disintegration component and measurement device which involves continuous acquisition of picture by CCD camera to record disintegration. Plastic cell divided in two parts; one component inner tank containing stirring bath, second compartment is outer tank of thermostated water | Medium 200 ml , temperature 37±2°C |

8. Dissolution Test

The development of dissolution methods for ODTs is comparable with the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for ODT much in the same way as conventional tablets. USP dissolution apparatus 1 and 2 can be used. USP 1 Basket apparatus may have certain applications, but sometimes, tablet fragments or disintegrated tablet masses may

become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. Kancke proposed USP 2 Paddle apparatus, which is the most suitable and common choice for ODTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of ODT is very fast when using USP monograph conditions; hence, slower paddle speeds may be utilized to obtain a profile. The USP 2 Paddle apparatus at 50 to 100 rpm is suitable for dissolution testing of taste-masked drug as well. The media used for the taste-masked drug should match that of the finished product to maximize the value of the test. High-performance liquid chromatography is often required to analyze dissolution aliquots due to presence of Ultraviolet (UV) absorbing components, specifically flavors and sweetener. Excipient to drug ratio may be higher since the formulation is designed to have good taste and mouth feel, decreasing the detection of the drug to background (excipient) in the UV spectrophotometer .

CONCLUSION

Fast dissolving drug delivery system have better patient compliance and may offer improved biopharmaceutical properties, improved efficacy and better safety compared with conventional oral dosage forms. FDT formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth. Many drugs can be incorporated in FDT especially unpalatable drugs. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and undertreated patient populations. Although the cost to manufacture these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer. 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 pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as fast dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. Rapid onset, good stability and increased bioavailability lead to its current growth in the market.

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