April 2014, Volume-5, Issue-2
Available Online at www.ijppronline.in

International Journal Of Pharma Professional's Research

Review Article

ISSN NO:0976-6723

TECHNOLOGIES INFLUENCING RAPIDLY DISINTEGRATING DRUG DELIVERY SYSTEMS: A REVIEW

Amit Alexander[1] *, D K Tripathi[1], Tapan K Giri[1], Junaid Khan[1], Vijendra Suryawanshi[2], Ravish J Patel[3]

1-Rungta College of Pharmaceutical Sciences and Research, Bhilai (C.G.), India.
2- ShriRawatpra Institute of Pharmacy, Kumhari, (C.G), India.
3-Ramanbhai Patel College of Pharmacy, Gujarat, India.

Abstract

Since the era of medicine has started every attempt has been made to facilitate the dose administration to the patient by achieving maximum efficacy. The evolution of rapidly disintegrating drug delivery systems had prove to be a milestone as they are designedto facilitate the administration of medication to patients who experience difficultyin swallowing (dysphagia) and for the convenience of all patients since the products may be administered at any time. Some tablets are also designed todissolve in saliva remarkably fast, within a few seconds,and are true fast-dissolving tablets. Others contain agentsto enhance the rate of tablet disintegration in the oralcavity, and are more appropriately termed rapidly disintegratingtablets, as they may take up to a minute tocompletely disintegrate.A number of other rapidly disintegrating oral technologies have been introduced in recent years, such as Lyoc (Laboratoires L. Lafon, MaisonsAlfort, France), Orasolv(CIMA Labs, Inc., Eden Prairie, MN), WOWTAB (Yamanouchi Pharma Technologies, Inc., Palo Alto, CA), and Flashtab (Ethypharm). These technologies help pharmaceutical companies to extend the life cycle of their products and to differentiate them in themarketplace.Rapidly disintegrating drug delivery systems have significant advantages of both solid and liquid dosage forms.

Keywords: -Fast Dissolving, mouth dissolving, zydis, cotton candy, flash tab, fast/rapidly disintegratingtablets..

Introduction

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration leads to high level of patient compliance. Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. [1] Novel technologies with improved performance, patient compliance, and enhanced quality have emerged in the recent past. [2] The term ‘‘oro-dispersible tablet” appears in the European Pharmacopoeia defined as ‘‘uncovered tablet for buccal cavity, where it disperses before ingestion”.[3]pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). There are two different types of dispersible tablets whichhave to be distinguished: one dosage form disintegrates instantaneously in the mouth, to be swallowed without the need for drinking water while the other tablet formulation can readily be dispersed in water, to form a dispersion, easy to ingest by the patient.[4] Mostfastdissolving delivery system (FDDTs) films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. These are also called melt-in-mouth tablets, repimelts, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets. The target populations for these new fastdissolving/ disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with persistent nausea, who are traveling, or who have little]

or no access to water are also good candidates for FDDTs. [5] The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant. An eightyear- old with allergies could use a more convenient dosage form than an 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 middleaged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker. Fast-dissolving/disintegrating tablets (FDDTs) are a perfect fit for all of these patients. [5]

Significance of Fast Dissolving Drug Delivery System

- Since these are unit dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
- Rapid absorption is achieved which causes rapid onset of action.
- Use of flavor and sweeteners in FDDDS can enhance the mouth feel property by reducing the 'bitter pill' medication.
- Travelling patients that do not have the availability of water can easily consume the drug without any obstruction.
- Some of the drug is absorbed from the mouth, pharynx and oesophagus as they move down and thus the bioavailability of that drug is increases.[6]
- Very much convenient to those class of patients who refuse to swallow a tablet, such as pediatric and geriatric patients and, psychiatric patients.
- As compared to liquid it is very much convenient to administer and having accurate dosing.
- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects. [5]

Properties of Ideal Rapidly Disintegrating Drug Delivery Systems.

They should -

• Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
• Allow high drug loading.
• Be compatible with taste masking and other excipients.
• Have a pleasing mouth feel.
• Leave minimal or no residue in the mouth after oral administration.
• Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
• Exhibit low sensitivity to environmental conditions such as humidity and temperature.
• Be adaptable and amenable to existing processing and packaging machinery.
• Allow the manufacture of tablets using conventional processing and packagingEquipments at low cost. [7]

Choice of Drug Candidate

Suitable drug candidate for orally disintegrating tablet should posses:

No bitter taste.
Good stability in water and saliva.
Dose should be low as possible.

Unsuitable drug candidate for orally disintegrating tablet should include:

Short half-life and frequent dosing.
Drug having very bitter taste.
Required controlled or sustained release. [8]

Hurdles to Develop Rapidly Disintegrating Drug Delivery Systems:

1. Rapid disintegration of tablet.
2. Avoid increase in tablet size.
3. Have sufficient mechanical strength.
4. Minimum or no residue in mouth.
5. Protection from moisture.
6. Good package design.
7. Compatible with taste masking technology.
8. Not affected by drug properties. [6]

Methodology Employed For FDT Formulations

Melt granulation

Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a binder which can be a molten liquid or a solid that melts during the process. [10] Melt granulation has been successfully applied to develop sustained release formulations, taste masked formulations with lipophillic melting binders, such as

glycerolmonostearate, a combination of a hydrophobic materials, a starch derivative and Stearic acid among others.[11]The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. [5]

Three-dimensional Printing (3DP)

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. The rapid disintegration of the tablets prepared by this method seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume. [12]

Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets.

Spray Drying

Maximum drug release and minimum disintegration time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

Cotton Candy Process

The FLASHDOSE® is a MDDDS (Mouth dissolving drug delivery system) manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as 'floss', made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

I. Floss Blend

"Floss Mix" is prepared by adding 80% sucrose in mannitol/dextrose blended with 1% surfactant. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

II. Floss Processing

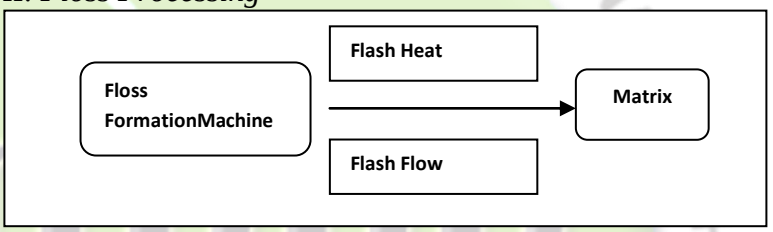

Fig. no.1: Formation of matrix by floss formation machine.

The floss formation machine uses flash heat and flash flow processes to produce matrixfrom the carrier material (*Fig.no.1)*.

The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature.

III. Floss Chopping and Conditioning

In this step the fibers are converted into smaller particles in a high shear mixergranulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss.

IV. Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug alongwith other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms

to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.[7]

Molding

The molding technology results in tablets with an appropriate dissolution time, even though they are characterized by poor mechanical properties (hardness).

Lyophilization or Freeze-Drying

Development of a lyophilized orally disintegrating tablet (ODT) that enhanced the in vitro dissolution and in vivo absorption of a drug with poor solubility and poor bioavailability is presented. [13] Freeze-drying allows immediate dissolution of the tablets because of their high porosity, and enhances drug stability, especially for moisture-sensitive substances; on the other hand, a porous network is associated with low physical resistance and high friability. Special packaging is required in some cases.

Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredientsis due to the low porosity of the tablets. Inert solid ingredients that volatilize readily(ammonia,sodium carbonate, hexamethelentetraamine camphor, etc.)were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures*(Fig.No.2)*. Additionally, several solvents (e.g. cyclohexane, benzene) can be also used as pore forming agents,

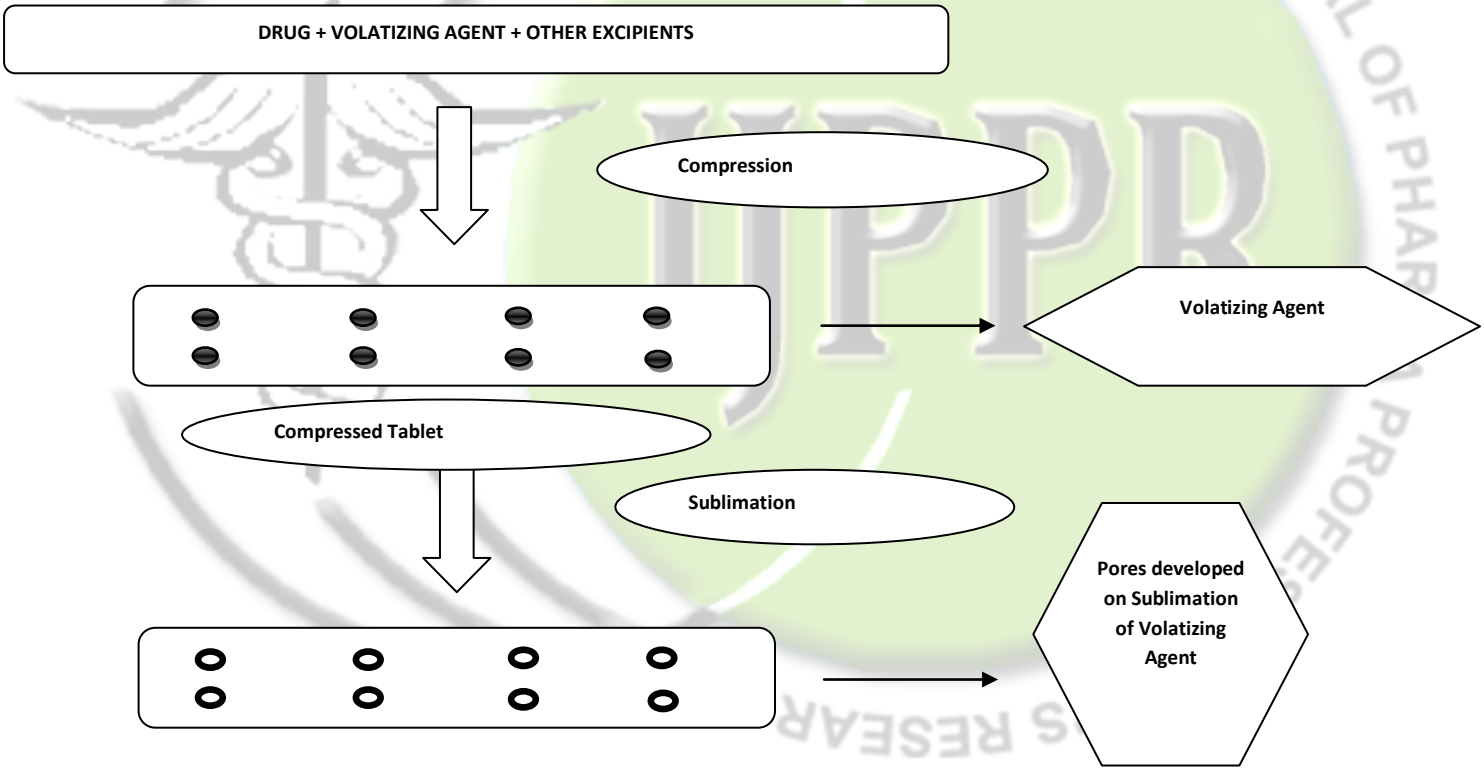

Fig. No.2: The volatile materials were removed via sublimation.

Drugs to be Promising in Corporated in Fast Dissolving Tablets*(Table.No.1)* [14]

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

Table.No.1: Drugs to be Promising in Corporated in Fast Dissolving Tablets[14]

Category	Drugs can be used
Analgesics and Anti-inflammatory Agents	Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, FenoprofenCalcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.
Anthelmintics	Albendazole, BepheniumHydroxynaphthoate, Cambendazole, Dichlorophen, Iverrnectin, Mebendazole, Oxarnniquine, Oxfendazole, OxantelEmbonate, Praziquantel, PyrantelEmbonate, 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, Tetracycline, Trimethoprim
Anti-coagulants	Dicoumarol, Dipyridamole, Nicoumalone, Phenindione. Anti-Depressants: Amoxapine, Ciclazindol, Maprotiline, Mianserin, Nortriptyline, Trazodone, Trimipramine Maleate., Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolazamide, Tolbutamide
Anti-Epileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid
Anti-Fungal Agents	Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Fiucytosine, 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, Minoxidii, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.
Anti-Malarials	Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate. Anti-Migraine Agents: DihydroergotamineMesyiate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate, Sumatriptan Succinate
Anti-Muscarinic Agents	Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine Butyl Bromide, Hyoscyarnine, Mepenzolate Bromide, Orphenadrine, Oxyphencylcimine, Tropicamide
Anti-Neoplastic Agents And Immunosuppressants	Aminoglutethimide, Amsacrine, Azathiopnne, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitotane, Mitozantrone, Procarbazine, Tamoxifen Citrate, Testolactone
Anti Protozoal Agents	Benznidazole, Clioquinol, Decoquinate, Diiodohydroxyquinoline, DiloxanideFuroate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.
Anti-Thyroid Agents	Carbimazole, Propylthiouracil
Anxiolytic, Sedatives, Hypnotics And	Alprazolam, Amyiobarbitone, Barbitone, Bentazeparn, Bromazepam, Bromperidol, Brotizoiam, Butobarbitone, Carbromal, Chlordiazepoxide,

Neuroleptics	Chlormethiazole, Chlorpromazine, Clobazam, Clotiazepam, Clozapine, Diazepam, Droperidol, Ethinamate, Flunanisone, Flunitrazepam, Fluopromazine, FlupenuiixolDecanoate, FluphenazineDecanoate, Flurazepam, Haloperidol, Lorazepam, Lormetazepam, Medazepam, Meprobamate, Methaqualone, Midazolam, Nitrazepam, Oxazepam, Pentobarbitone, PerphenazinePimozide, Prochlorperazine, Suipiride, Temazepam, Thioridazine, Triazolam, Zopiclone
Tj-Blockers	Acebutolol, Alprenolol, Atenoiol, Labetalol, Metoptolol, Nadolol, Oxprenolol, Pindolol, Propranolol
Cardiac Inotropic Agents	Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin
Corticosteroids	Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate, Desoxymethasone, Dexamethasone, Fludrocortisone Acetate, Flunisolide, Flucortolone, Fluticasone Propionatu, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone
Diuretics	Acetazolarnide, Amiloride, Bendrofluazide, Bumetanide, Chlorothiazide, Chlorthalidone, Ethacrynic Acid, Frusemide, Metolazone, Spironolactone, Triamterene. **Enzymes** : All The Enzymes
Anti-Parkinsonian Agents	BromocriptineMesylate, Lysuride Maleate
Gastro-Intestinal Agents	Bisacodyi, Cimetidine, Cisapride, Diphenoxylate, , Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron, Ranitidine, Sulphasaiazine
Histamine H,-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, GlycerylTrinitrate, IsosorbideDinitrate, IsosorbideMononitrate, PentaerythritolTetranitrate.
Nutritional Agents	Betacarotene, Vitamin A, Vitamin B_2 , Vitamin D, Vitamin E, Vitamin K.
Opioid Analgesics	Codeine, Dextropropyoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine
Oral Vaccines	For Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, Hiv, Aids, Measles, Lyme Disease, Travellers Diarrhea, Hepatitis A, B And C, Otitis Media, Dengue Fever, Rabies, Parainfluenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhegic Fever, Argentina Haemorrhagic Fever, Caries, Chagas Disease, Urinary Tract Infection Caused By E.Coli, Pneumoccoccal 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 To 300,000), Calcitonins And Synthetic Modifications Thereof, Enkephalins, Interferons (Especially Alpha-2 Inter Feron For Treatment Of Common Colds)
Sex Hormones	Clomiphene Citrate, Danazol, Ethinyloestradiol, Medroxyprogesterone Acetate, Mestranol, Methyltestosterone, Norethisterone, Norgestrel, Oestradiol,

	Conjugated Oestrogens, Progesterone, Stanozolol, Stiboestrol, Testosterone, Tibolone
Stimulants	Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mhazindol, pemoline
Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mhazindol, 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. Optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.	

Mechanism of Superdisintegrants: There are four major mechanisms for tablets disintegration as follows

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

2. Porosity and capillary action (Wicking): Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles

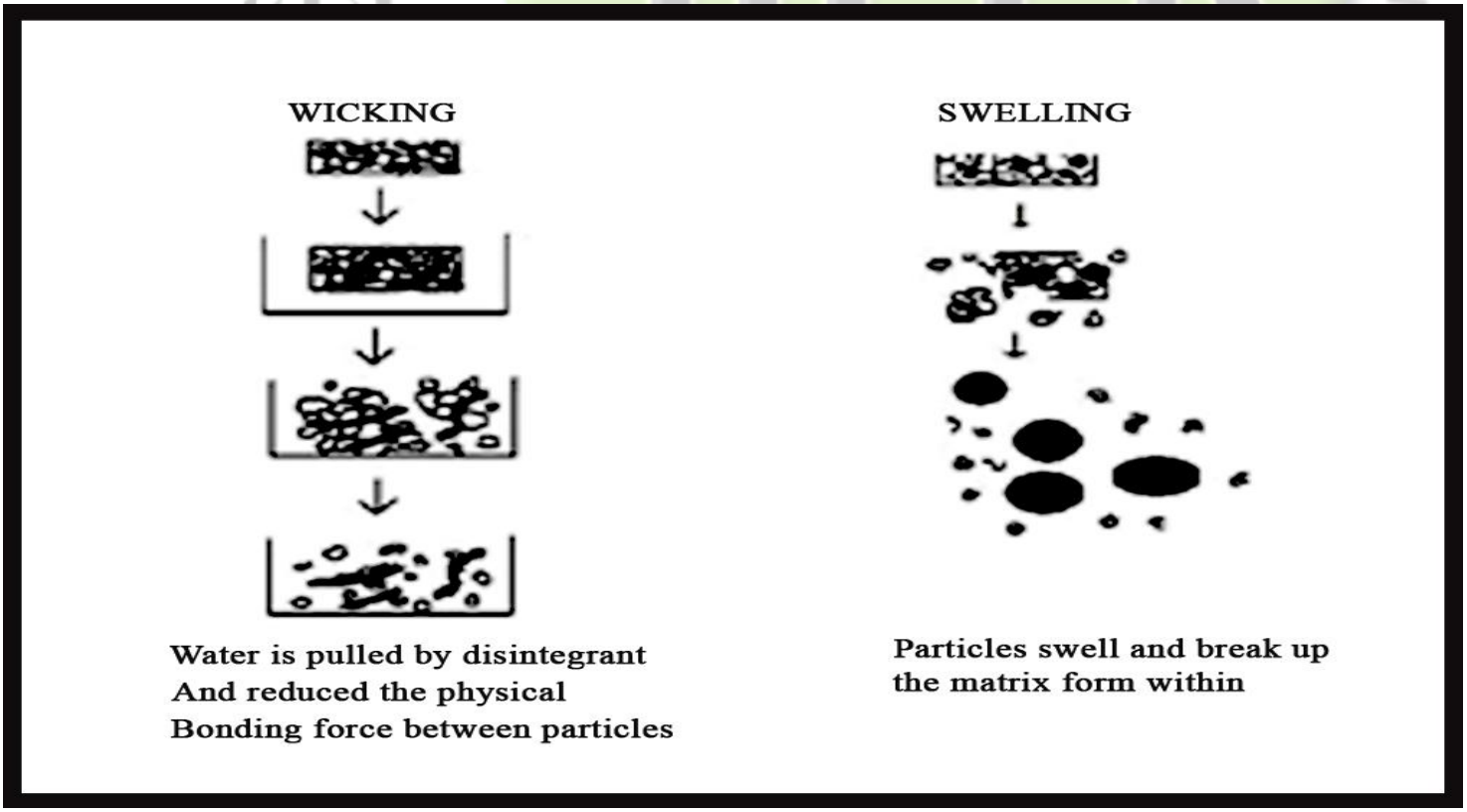

Fig. no.3: Mechanism of Superdisintegrants: Porosity and capillary action (Wicking)

3. Due to disintegrating particle/particle repulsive forces: Another mechanism of disintegratn attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

4. Due to deformation: During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water*(Fig.No.4)*. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

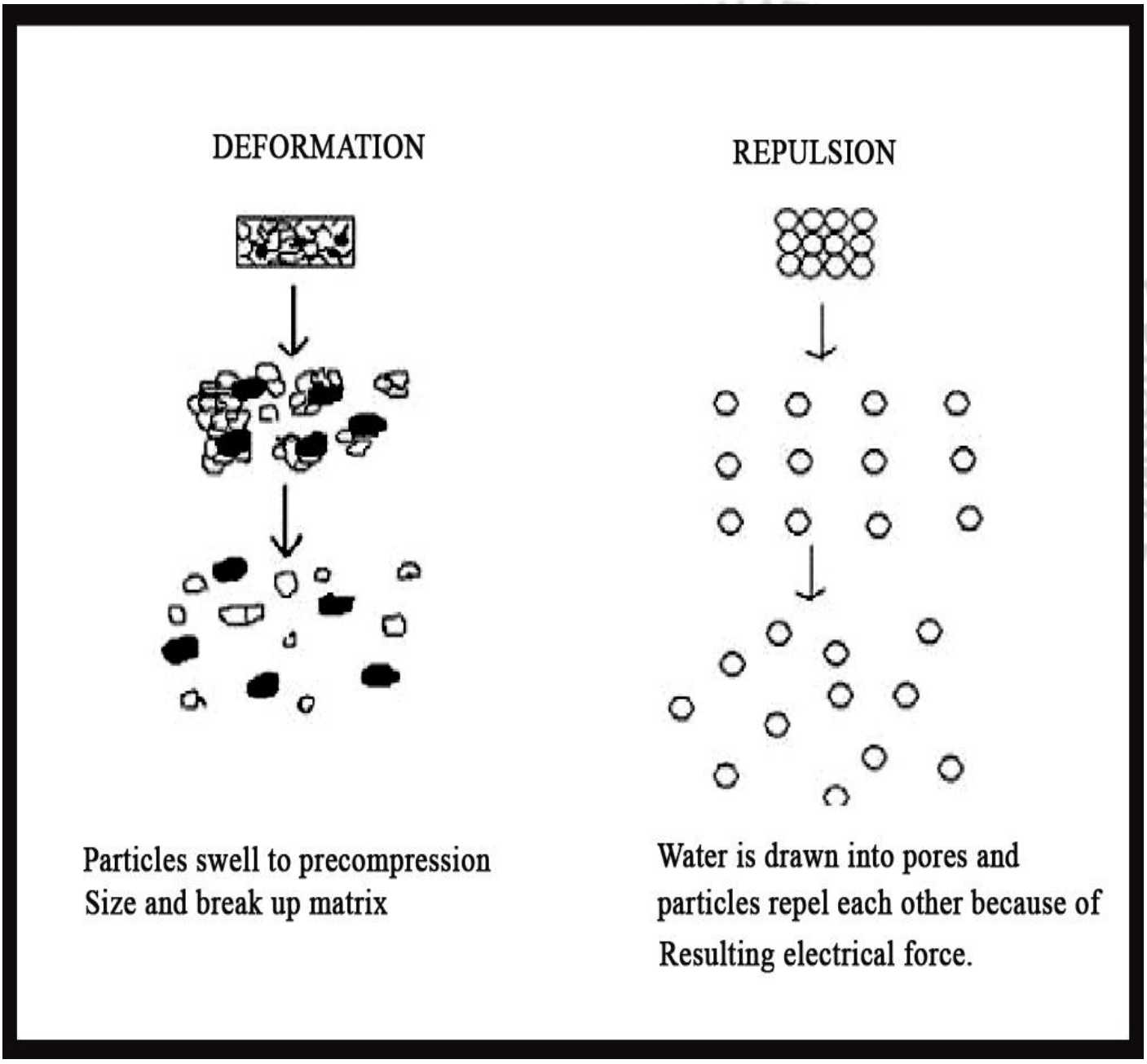

Fig. no.4: Mechanism of Superdisintegrants: deformation

There are various polymers available that are used as a superdisintegrants which are mention below in Table.No.2

Table -2:list of super disintegrants. **[15]**

Superdisintegrants	Example	Mechanism of action	Special Comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab® Vivasol®L-HPC	Crosslinked cellulose	Swells 4-8 folds in< 10 seconds. -Swelling and wicking both.	Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	Swells very little andreturns to original size aftercompression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		Does not contain any starch or sugar. Used in nutritionalproducts.
Calcium silicate		Wicking action	Highlyporous,Optimum concentration is between 20-40%

PATENTED TECHNOLOGIES FOR FAST DISSOLVING TABLETS

ZYDIS (R.P. Scherer, Inc.)

Description Of The Dosage Form And Mode Of Drug Release

Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the characteristically high porosity produced by the freeze-drying process used in its manufacture. The highly porous structure allows the rapid ingress of saliva, which quickly dissolves the soluble excipients, releasing the drug particles as a suspension or solution on the tongue. The suspen- sion is then swallowed and the drug absorbed in the normal way. Human in vivo studies, using gamma scintigraphy, have shown that even when taken without water, the component materials of the formulation uniformly disperse over the mucosa and are subsequently cleared efficiently from the buccal and esophageal region. In some cases, depending on the characteristics of the drug, absorption can take place within the oral cavity.

Zydis Oral Fast-Dissolving Dosage Form: The crystal structure that determines the porosity of the final

other technologies listed utilize either dry-powder compression techniques or molding processes to produce the tablet forms, and rely on the fast disintegrating properties of the excipients to produce the spontaneous dispersion in the mouth. These processes produce tablets that are more dense and therefore significantly less porous than the Zydis form, resulting in slower disintegration times, typically 30–60 s. Fast-melt forms made by compression are significantly more friable than conventional tablets and so require special single-dose unit packaging.

ZYDIS MANUFACTURING PROCESS: The commercial Zydis manufacturing process, schematically outlined in Figure5, consists of the steps described below.

a. **Preparation of Drug Suspension/Solution:** A vacuum mixer is used to first prepare the aqueous solution of excipients andthen to add and disperse the active ingredient by high shear homogenization.Once prepared, the solution or dispersion is transferred to a holding vessel.
b. **Forming-Filling:** The drug suspension is circulated from the holding vessel through a manifoldsupplying a series of positive displacement pumps. These pumps deliver the re-quired volume of material along the delivery lines into the blister pockets, whichare preformed in a continuous ribbon of plastic laminate.

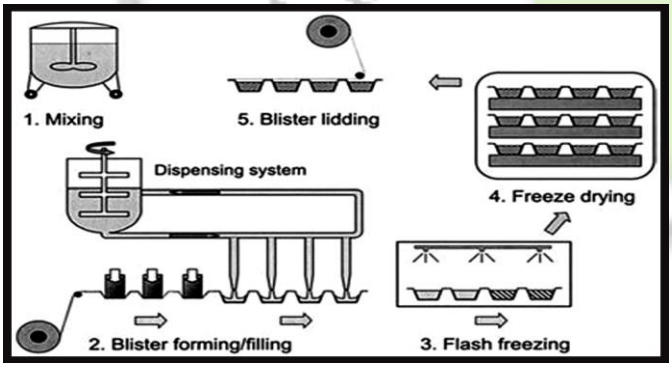

Fig. no.5: Schematic of the Zydis manufacturing process.

c. **Freezing:** After the blister pockets are filled, the blister ribbon is cut into short lengths,called "trays," which are transferred on a conveyor through the freeze tunnel.The cold nitrogen atmosphere freezes the product within minutes. This "flash"freezing "fixes" the homogeneity of the components and creates the appropriateice product. The frozenproduct is collected and transferred to a series of refrigerated storage cabinets tomaintain it in the frozen state prior to loading into the freeze dryer.
d. **Freeze Drying:** The "trays" containing the frozen product are loaded onto the shelves of thefreeze dryer and the ice removed by sublimation at low pressure. The dryers arecharacterized by a short intershelf spacing, which maximizes the product loadingand accelerates the drying process. Typical drying times are on the order of 5 h.
e. **Blister Lidding:** The dried product is then sealed into the blister pockets by application of thelidding foil and the blister pack is then punched out to the required format.[15]

DURASOLV (Cima Labs, Inc.)

ORASOLV

The time for the disintegration of OraSolv tablets within the oral cavity varies from 6 s to 40 s, depending largely on tablet size and the compression force (within the lower range) that was used to form the tablet. The low compression force leads to high tablet porosity which, in turn, accelerates the rate of disintegration of the tablet and dissolution of the water-soluble excipients. The active ingredients can be taste-masked using a variety of techniques such as fluid bed coating, microencapsulation, or spray congealing. Because the OraSolv tablets are produced at low compression forces, they are soft and friable. To reduce handling of the tablets, the tableting and packaging processes are integrated and a specially designed package is used. The packaging system consists of a robot that picks up and places the tablets in dome-shaped depressions in aluminum foil. A layer of top foil is heat-sealed over the bottom foil. The integrated manufacturing line is equipped with a printing assembly that enables each blister card to be printed individually during the manufacturing process. The automated system then cuts the foil into cards of, usually, six tablets.Arobot eye detects depressions that do not contain tablets and rejects these cards. The operator may also observe unfilled cards on a monitor. The specially designed package and processing system, referred to as Pak-Solv, protects the OraSolv tablets from breaking and attrition during the rigors of shipping. In particular, the dome-shaped depressions limit the vertical movement of the tablet within the package since the diameter of the lower portion of the dome is too narrow to accommodate the tablet. Thus the tablet remains in the upper part of the dome adjacent to the top foil. This is in contrast to a regular blister package in which the sides of the depression are vertical and the bottom is flat, allowing a greater range of vertical movement. PakSolv also offers light, moisture, and child resistance. Moisture resistance is important when packaging an effervescent formulation or moisture-sensitive drugs.

avoided, only small amounts of effervescent agents may be

DuraSolv is Cima's second-generation fast-dissolving tablet technology. Like OraSolv, the Dura Solv tablets consist of water-soluble excipients and are manufactured using direct compression techniques. However, DuraSolv utilizes nondirectly compressible fillers in fine particle form these fillers have a high surface area, which increases their dissolution rate. The incorporation of a high proportion of such fillers causes the tablet to "melt" or dissolve, rather than disintegrate. Wicking agents assist the entry of water into the body of the tablet, whereas swelling disintegrants are avoided or used in small proportions. Since extensive disintegration is to be incorporated, if they are to be included at all. The limited disintegration contributes to the nongritty mouth feel conferred on the product by the use of fine-particle fillers. The increased dissolution rate of the soluble, fine-particle filler compensates for the reduction in tablet porosity due to the use of higher compression forces (relative to the OraSolv products). The manufacturing process utilizes conventional blenders and high-speed tablet presses. DuraSolv tablets are robust and conventional packaging equipment can be used to package theminto bottles. The product may also be packaged into blisters or pouches, if desired.

Commercial products manufactured according to CIMA LABS' technologies are listed in Table 3.

Table 3: Currently Marketed Intraorally Disintegrating Tablets Manufactured byCIMA LABS Inc.

PRODUCT	**ACTIVE INGREDIENTS**
Tempra* FirsTabs	Acetominophen 160 mg
Triaminic® Softchew™ Coldand Allergy	Pseudoephedrine HCl 15 mg, chlorpheniramine maleate 1 mg
Triaminic®Softchews™ Cold and Cough	Pseudoephedrine HCl 15 mg, dextromethorphan HBr monohydrate 5 mg, chlorpheniramine maleate 1 mg
Triaminic®Softchews™Throat Pain and Cough	Acetominophen 160 mg, pseudoephedrine HCl 15 mg
Triaminic®Softchews™Cough	Dextromethorphan HBr monohydrate 7.5 mg
Triaminic®Softchews™allergy sinus + headache	Pseudoephedrine HCl 15 mg, acetaminophen 160 mg
Triaminic®Softchews™ allergy congestion	Pseudoephedrine HCl 15 mg
NuLev ™	Hyoscyamine 0.125 mg
Zomig-ZMT™ 2.5 mg	Zolmitriptan 2.5 mg
Zomig-ZMT® 5 mg	Zolmitriptan 5 mg
Remeron® SolTab™	Mirtazipine 15 mg
Remeron® SolTab™	Mirtazipine 30 mg
Remeron® SolTab™	Mirtazipine 30 mg

WOWTAB (Yamanouchi PharmaTechnologies, recently announced the filing of an NDA for a FlashDose

Inc.)

Wowtab technology was developed by Yamanouchi Pharma Technologies. 'Wow' means 'without water'. The active ingredients may constitute upto 50% w/w of the tablet. Here, saccharides of both low and high Moldability are used to prepare the granules. Moldability is the capacity of a compound to be compressed. Highly Moldable substance has high compressibility and thus slow dissolution. The combination of high and low Moldability is used to produce tablets of adequate hardness & a rapidly melting strong tablet. Active ingredients are mixed with low Moldability saccharides and then granulated with high Moldability saccharides and then compressed into tablet. Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packs. This technology utilizes conventional granulation and tableting methods and used for both water-soluble and insoluble drugs. The manufacturing process involves granulating low-moldable sugars (e.g. mannitol, lactose, glucose, sucrose, and erythritol) that show quick dissolution characteristics with high moldable sugars (e.g. maltose, maltitol, and sorbitol). The result is a mixture of excipients that have fast-dissolving and highly moldable characteristics [8]

OTHER TECHNOLOGIES NOT YET ON THE U.S. MARKET

FlashDose (Fuisz Technologies, Ltd.), Flashtab (Prographarm Group), and OraQuick (KV Pharmaceutical Co., Inc.) are three formulations on the worldwide market which will likely reach the United States in the near future. Biovail Corp version of zolpidem tartrate. These technologies are similar to Zydis, WOWTAB, OraSolv and DuraSolv in that they dissolve or disperse on the tongue within a minute. However, each also has unique characteristics to differentiate itself from the competition.

FLASHDOSE (Fuisz Technologies, Ltd.)

Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development, FlashDose. The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres hasbeen patented by Fuisz, and is known as CEFORM1 and serves as an alternative method of taste masking.

FLASHTAB (Prographarm Group)

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. All the processing utilized conventional tableting technology.

***Table . No.4: List of commercially Available Fast dissolving tablets*[17]**

TRADE NAME	ACTIVE DRUG	MANUFACTURER
Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Zofran ODT	Ondansetron	GlaxoWellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zeplar TM	Selegilline	Amarin Corp., London, UK
TempraQuiclets	Acetaminophen	Bristol myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
Olanexinstab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA

ORAQUICK (KV Pharmaceutical Co., Inc.)

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

ADVANTOL™ 200

Advantol™ 200 is a directly compressible excipient system offering "Soft-Melt" functionality and specially formulated for nutraceutical applications. SPI Pharma'sAdvantol platform uses proprietary co-processing technology. Advantol requires no special manufacturing equipment or tooling. Advantol formulations utilize a standard rotary tablet press with standard tooling under normal tableting temperature and humidity conditions to make robust "soft-melt" tablets.

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.

ADVATAB

AdvaTab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. AdvaTab is distinct from other ODT technologies as it can be combined with Eurand's complimentary particle technologies like its world leading Microcaps® tastemasking technology and its Diffucaps® , controlled release technology. The pairing of AdvaTab with Microcaps creates products that offer the dual advantageof a patient preferred dosage form, together with a superior taste and smooth mouth feel. This is a critical advantage as the unpleasant taste of drugs is a significant restriction in the application of other ODT technologies.

REFERENCES

1. Nagendra D, Raju SA, Fast Dissolving Tablets of FesciencesxofenadineHCl by Effervescent Method. Indian J. Pharm. Sci.,2009; 71(2):116.
2. SastryS V, NyshadhamJ R, Recent technological advances in oral drug delivery, Pharmaceutical Science & Technology Today 2000;3(4):138.
3. FiniA, Bergamante V, Fast dispersible/slow releasing ibuprofen tablets, European Journal of Pharmaceutics and Biopharmaceutics. 2008;69:335.
4. SchiermeierS, Schmidt P, Fast dispersible ibuprofen tablets, European Journal of Pharmaceutical Sciences, 2002;15:295.
5. Patel P B, Fast Dissolving Drug Delivery Systems: An Update, Pharmainfo.net, 2006;4(4)
6. Bandari S, Gannu R, Orodispersile Tablets: An Overview, Asian Journal of Pharmaceutics, 2008;2-10.
7. Shukla D, Chakraborty S, Mouth Dissolving Tablets I:An Overview of Formulation Technology, Sci Pharm. 2009; 76; 309–326.
8. Wagh*et al.* Techniques used in orally disintegrating drug delivery system. International Journal of Drug Delivery 2,2010; 98-107
9. Bhoyar, et al. J Young Pharm. 2010;2(3):240-246.
10. Amrutkar*et al.* Design and evaluation of taste masked chewable dispersible tablet of lamotrigine by melt granulation, International Journal of Drug Delivery 2, 2010; 183-191.
11. Bhupendra G Prajapati*et al*, A Review on Recent patents on Fast Dissolving Drug Delivery System, Int.J. PharmTech Res, 2009;(3):1-6.
12. ShoukriR A, Ahmed I S, In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets, European Journal of Pharmaceutics and Biopharmaceutics, 2009;73:162-171.
13. Shailesh S, New Generation of Tablet: Fast Dissolving Tablet, Pharmainfo.net, 2008;6(1).
14. D Bhowmiket al, Fast Dissolving Tablet: An Overview, Journal of Chemical and Pharmaceutical Research, 2009, 1(1): 163-177.

CORRESPONDENCE ADDRESS:
Amit Alexander
Rungta College of Pharmaceutical Sciences and Research, Bhilai (C.G.), India. PH: 09907333846 E-mail: mailme_amitalex@yahoo.in-Most