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# A REVIEW ON "NOVEL CONCEPT OF ORAL FAST DISSOLVING TABLET"

Pathan V. T.*, Rane B. R., Gujarathi N. A., Bakliwal S. R., Pawar S. P.

**Affilfiation:**

P.S.G.V.P.Mandal's, College of Pharmacy, Department of Pharmaceutics, Shahada, Maharashtra.

## ABSTRACT

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and h case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance1.To overcome these drawbacks, mouth dissolving tablets (MDT) or orally disintegrating tablets; (ODT) has emerged as alternative oral dosage forms. These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds'. According to European Pharmacopoeia, the ODT should disperse / disintegrate in less than three minutes. The basic approach used in development of MDT is the use of superdisintegrants like Cross linked carboxymelhylcellulose (Croscarmeliose), Sodium starch glycolate (Primogel, Explotab). Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to the standard tablets.

***Key Words:*** *Fast Dissolving Tablet, Direct compression, Super-disintegrants, Lyophilization*

## INTRODUCTION

A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintregrants in the oral cavity without the need of water or chewing. Most fast-dissolving delivery system 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, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets *[1]*.

**An ideal Properties of FDT**

It is not required water for oral administration, yet dissolve /disperse/ disintegrate in mouth in matter of seconds. Have a pleasing mouth feel. Have an acceptable taste masking property. Be harder and less friable Leave minimal or no residue in mouth after administration Exhibit low sensitivity to environmental conditions (temperature and humidity). Allow the manufacture of tablet using conventional processing and packaging equipments*[2]*.

**Advantages of FDT**

Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients. It achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down. It was convenient for administration and patient compliance for disabled, bedridden patients and for travelers and busy people, who do not always have access to water. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients & the risk of chocking or suffocation during oral administration *[3]*.

**Selection of Drugs**

The ideal characteristics of a drug for in vivo dissolution from an FDT include

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (log P>1, or preferably>2)
- Ability to permeate oral mucosal tissue

Unsuitable drug characteristic for FDT;

- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release

To overcome these drawbacks, mouth dissolving tablets (MDT) or orally disintegrating tablets; (ODT) has emerged as alternative oral dosage forms. These are the unique type of tablets that disintegrate or dissolve or disperse in salivary fluid within few seconds'. According to official publication

European Pharmacopoeia the ODT should be disperses or disintegrates in less than three minutes. The fundamental approach used in development of ODT is the use of superdisintegrants like Sodium starch glycolate, (Primogel, Explotab) carboxymelhylcellulose (Croscarmeliose),. Polyvinylpyrrolidone (Polyplasdone) etc. which provides rapid disintegration of tablet after putting in mouth, and release the drug in saliva. Bioavailability of certain drugs may be increased due to absorption of drugs in oral cavity and may be due to pregastric absorption of saliva which contains dispersed drugs which pass down into the stomach. The amount of drug which is subject to undergo first pass metabolism is reduced *[4]*.

**Biopharmaceutical Consideration**

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

**Pharmacokinetics:**

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

**Pharmacodynamics:**

Drug receptor interaction impaired in elderly as well as in young adult due to undue development of organ. Decreased ability of the body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin thus decreased sensitivity of the CVS to β-adrenergic agonist and antagonist. Immunity is less and taken into consideration while administered antibiotics. Altered response to drug therapy-elderly show

diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed. Research workers have clinically evaluated drug combination for various classes of drug like cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patient *[5]*.

**THE NEED FOR DEVELOPMENT OF FAST DISINTEGRATING TABLET**

The need for non-invasive delivery systems persists due to poor acceptance and compliance of the patients with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

**1. Patient factors**

Fast disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with water. These include the following:

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Travelling patients suffering from motion sickness and diarrhoea that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H2 blockers, which are prescribed in order to avoid gastric ulceration.
- Mentally challenged patients, bedridden patients and psychiatric patients. *[6]*

**2. Effectiveness factor**

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT *[7].*

**3. Manufacturing and marketing factors**

As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and undertreated patient populations *[8]*.

**CHALLENGES IN FORMULATION OF FAST DISINTEGRATING TABLETS (FDTS)**

**1. Mechanical strength and disintegration time:**

It is obvious that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential. FDTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge *[9]*.

**2. Taste masking:**

As most drugs are unpalatable, rapid disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patients oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes essential to patient compliance *[10]*.

**3. Aqueous solubility:**

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process and it can be prevented by using various matrix-forming excipients such as mannitol which, have ability to induce crystallinity and hence, impart rigidity to the amorphous composite *[11]*.

**4. Hygroscopicity:**

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging. *[12]*

**5. Amount of drug:**

The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when

formulating a fast-dissolving oral films or wafers *[13]*.

**6. Size of tablet:**

It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve *[13]*.

**7. Mouth feel:**

FDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDTs should be as small as possible. Moreover addition of flavors and cooling agents like menthol improve the mouth feel *[13, 14]*.

**8. Sensitivity to environmental conditions:**

FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water *[14]*.

**Conventional Techniques used for preparation of Fast Dissolving Drug Delivery System**

**Disintegrant Addition**

Disintegrant addition technique is one of popular techniques for formulating Fast-dissolving tablets because of its easy implementation and cost-effectiveness. The basic principle involved in formulating Fast-dissolving tablets by disintegrant addition technique is addition of superdisintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel. Microcrystalline cellulose and low substituted hydroxyl propyl cellulose were used as disintegrating agents in the range of 8.2 – 9.1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Rapidly disintegrating tablets of bitter drugs oxybutynin & pirenzepine were prepared by using the taste masked granules and h mixture of excipients consisting of crystalline cellulose (Avicel PH 0-2) and low-substituted hydroxypropyl cellulose HPC, LH-11), Ishikawa et al. prepared rapidly disintegrating tablets using microcrystalline cellulose (Avicel PH-M series) that was spherical and had a very small particle size 7-32 um). instead of conventional microcrystalline cellulose (PH 10.2) Tablets prepared using microcrystalline cellulose; PH-M06 and L-HPC in the ratio of 9:1 were very rapidly disintegrating) in saliva. They concluded that Avicel PH-M06 was superior to Avicel PH 102 in terms of the feeling of roughness in the mouth. Fast dissolving table of efavirenz (anti HIV agent) were formulated by using combination of microcrystalline cellulose and sodium starch glycolate as super

disintegrant. Gillis et al, prepared a fast-dissolving tablet of galanthamine hydrobromide which comprises of spray dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, a cross linked polymeric disintegrant such as cross povidone and with a direct compression process of preparing such fast-dissolving tablets. Fast-dissolving tablets having analgesic activity was formulated using a combination of superdisintegrants. Rapid oral disintegration tablets were developed by direct compression using co-ground mixture of D-mannitol and crospovidone.

CIMA labs patented Orasolv technology by employing the evolution of carbon dioxide or the effervescence as disintegration mechanism in the formulation of fast-dissolving tablets. The OraSolv technology is an oral dosage form, which combines taste-masked drug ingredients with a quick dissolving effervescent excipient system.

Taste masking is achieved through a process of microencapsulation, which coats or entraps the active compound in an immediate release matrix. The effervescent excipient system aids in rapid disintegration of the tablet, permitting swallowing of pharmaceutical ingredients before they come in contact with the taste bud. The OraSolv tablet dissolves quickly without chewing or without water and allows for effective taste masking of a wide variety of active drug ingredients, both prescription and nonprescription. Flashtab technology™ is a patented technology of Prographarm, which employ combination of taste-masked multiparticulate active drug substances, a disintegrating agent, a swelling agent and other excipients to form a multiparticulate tablet that disintegrates rapidly. Rapidly disintegrating multiparticulate tablet was prepared by using taste-masked microcrystals of drugs, crosslinked disintegrating agent and soluble diluent with binding properties.

**Freeze Drying**

It is a process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

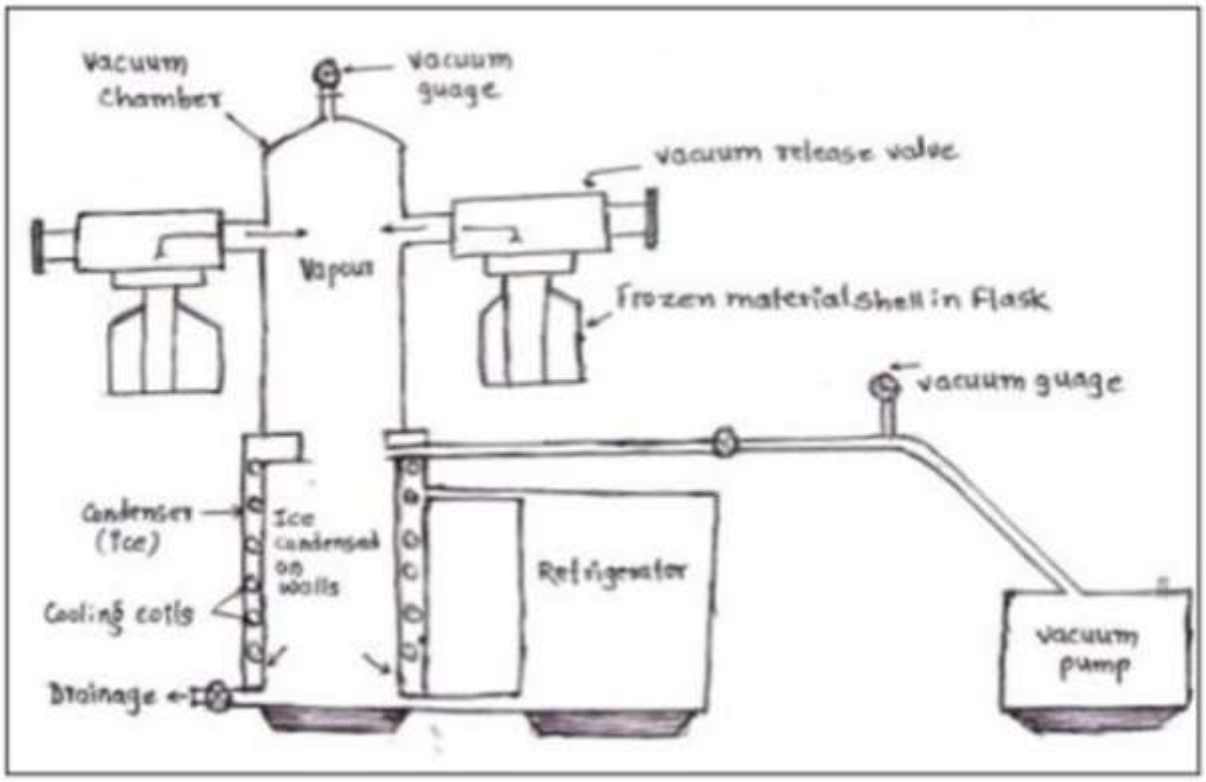


**Figure 1: Schematic Diagram of Freeze-drying Technique for Preparation of FDT**

**Moulding**

Tablet produced by molding are solid dispersion. Molded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is generally made from water soluble sugars. The active ingredient in most cases is absorbed through the mucosal lining of the mouth. The manufacturing process of molding tablets involves moistening the powder blend with a hydro alcoholic solvent followed by pressing into mold plates to form a wetted mass (compressing molding). The solvent is then removed by air drying. Thus the process is similar to what is used in the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution. Molded forms are also prepared using a heat-molding process that involves setting the molten mass that contains a dispersed drug. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at -300C under vacuum. Another process used is called no-vacuum lyophilisation, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure. Pebley et al., evaporated a frozen mixture containing a gum (e.g., acacia, carageenan, guar, tragacanth, or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol, or maltodextrin),

and a solvent in a tablet shaped mould. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

**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 crosscarmellose 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.

**Mass-Extrusion**

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste *[15, 16]*.

**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.

**Sublimation**

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed by Heinnemann & Rose, et al[24]. 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.

A method of producing fast dissolving tablet using water as the pore forming material has been described by Makino, et al. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Koizumi, et al, have developed a new method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a

subliming material. 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 table[25,26]. The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.

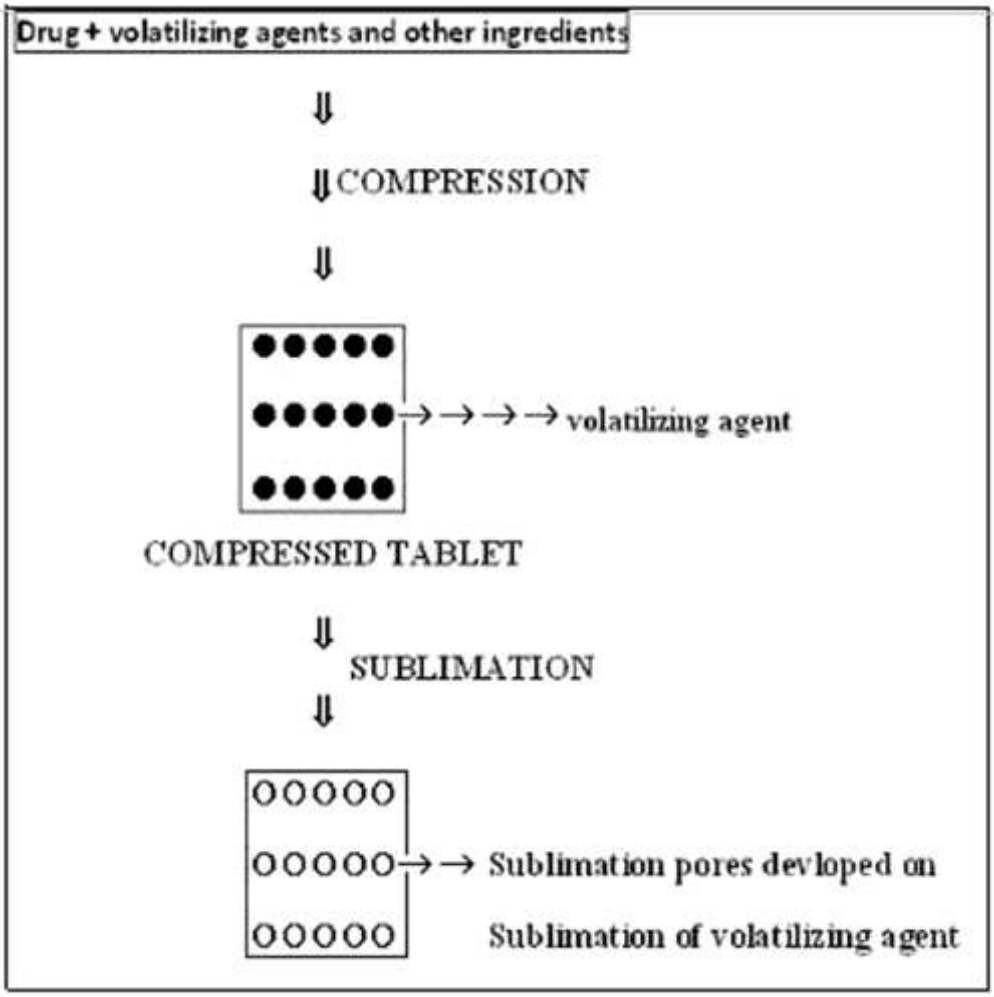


**Figure 2: Schematic Diagram of Sublimation Technique for Preparation of FDT *[15,16, 17]***

**Promising Drugs to be incorporated for Fast Dissolving Formulations**

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**:

Aloxiprin, 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, Iverrnectin, Mebendazole, Oxarnniquine, 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, 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: Dihydroergotamine Mesyiate, 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 & 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, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.

**Anti-Thyroid Agents:**

Carbimazole, Propylthiouracil.

**Anxiolytic, Sedatives, Hypnotics and Neuroleptics:**

Alprazolam, Amyiobarbitone, Barbitone, Bentazeparn, Bromazepam, Bromperidol, Brotizoiam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Clobazam, Clotiazepam, Clozapine, Diazepam, Droperidol, Ethinamate, Flunanisone, Flunitrazepam, Fluopromazine, Flupenuiixol Decanoate, Fluphenazine Decanoate, Flurazepam, Haloperidol, Lorazepam, Lormetazepam, Medazepam, Meprobamate, Methaqualone, Midazolam, Nitrazepam, Oxazepam, Pentobarbitone, Perphenazine Pimozide, Prochlorperazine, Suipiride, Temazepam, Thioridazine, Triazolam, Zopiclone.

**Beta-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:**

Bromocriptine Mesylate, 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 & other Anti-Anginal Agents:**

Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate.

**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:**

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 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. 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 *[18, 19, 20]*

**Excipients commonly used for ODT preparation.**

It contains active principle, mixture of excipients comprising at least one disintegrant, a diluent, a lubricant, and, optionally, a swelling agent, a permeabilizing agent,sweeteners, and flavorings.

Table 1: Name and weight percentage of different excipients

| Name of Excipient | Percentage used |
|---|---|
| Disintegrant | 1 to 15% |
| Diluent | 0 to 85% |
| Binder | 5 to 10% |
| Antistatic agent | 0 to 10% |

Binders commonly used are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulosic polymers it will be advantageous to select ethylcellulose, hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures, and the most commonly acrylic polymers are used are the ammonio-methacrylate copolymer (Eudragit. RL and RS), polyacrylate (Eudragit NE), and polymethacrylate (Eudragit. E).

Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols, and, preferably, mannitol. The most common antistatic agents used are colloidal silica (Aerosil), precipitated silica (Sylod. FP244), micronized or non-micronized talc, maltodextrins, .beta.-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearylfumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling. *[21, 22]*

**Super-Disintegrants and ODT**

Super-disintegrant plays the major role in orodispersible tablet. Caramella et al. found that disintegration efficiency is based on the force-equivalent concept (the combined measurement of swelling force development and amount of water absorption)5, 6. Force equivalence expresses the capability of a disintegrant to transform absorbed water into swelling (or disintegrating) force3. The optimization of tablet disintegration is commonly done by mean of the disintegration critical concentration. Below this concentration the tablet disintegration time is inversely proportional to the disintegrant concentration. Above the critical concentration, the disintegration time remains approximately constant or even increased. Common disintegrants used in this formulation are croscarmellose sodium (Vivasol, Ac-Di-Sol), crospovidone (Polyplasdone), carmellose (NS-300), carmellose calcium (ECG-505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found tohave super-disintegrant property and are widely used in pharmaceutical industry8. Swelling index of the super-disintegrants is commonly studied in simulated saliva. Volume occupied by the material at the end of 4 h should be noted and swelling index is calculated by the formula: (final volume-initial volume/initial volume) X 1008 *[23, 24, and 25]*.

**Taste-Masking of ODT**

Taste-masking of bitter or with objectionable tasting drug substances is critical for any orally-administered dosage form. Less commonly, active pharmaceutical ingredients

to be incorporated are tasteless and do not require taste masking. There are multiple approaches of taste masking of bitter drugs for ODT9.A drug solution or suspension can be applied to a substrate fallowed by polymer coating. _ Drug particles are coated directly by granulation of the drug with certain excipients fallowed by the polymer coating. Coating polymer concentration generally used ranges from 5 to 50 % (the percentages being expressed by weight relative to the weight of the coated granule). If the concentration of the polymer is less than 5% coating is not sufficient to allow effective masking of the taste. For a concentration greater than 50% the release of the active pharmaceutical ingredients is excessively retarded.

Drug particle coatings can vary in thickness, and certain polymer coating have pH-dependent solubility such as methacrylates which influence dissolution profiles. The coatings can dissolve, swell, or become permeable during the dissolution test depending on the selected media. Coating for controlled-release can also be used and incorporated into fast-dissolve dosage forms since compression force are low and the controlled-release particles remain intact. If the drug is tasteless or very low dose, direct blend of bulk drug substance into fastdisintegrating matrix is straightforward.Common sweetener is selected from the group comprising in particular aspartame, acesulfam potassium, potassium saccharin ate, neohesperidine dihydrochalcone, sucralose, monoammonium glycyrrhizanate.

Bitter drugs like roxithromycin and dicyclomine hydrochloride were taste masked using ion exchange resins *[26, 27, 28, and 29]*.

**EVALUATION OF FAST DISINTEGRATING TABLETS:** Tablets from all the formulation were subjected to following quality control test.

**1. General Appearance:** The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance and tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

**2. Size and Shape:** The size and shape of the tablet can be dimensionally described, monitored and controlled.

**3. Tablet thickness:** Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

**4. Hardness:** Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

**5. 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 height of 6 inches in each revolution. Pre -weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. The friability (F) is given by the formula.

$$F = W^{int.} - W^{fin.}$$

Where, Wint - Weight of tablets before friability.

$W^{fin.}$ - Weight of tablets after friability.

**6. Wetting Time:** Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured.

**7. Water absorption Ratio:** A piece of tissue paper folded twice was placed in a small Petridish 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,

$$R = 10 (wa/wb)$$

Where, **wa** is weight of tablet before water absorption & **wb** is weight of tablet after water absorption.

**8. In vitro dispersion time:** In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

**9. In vitro Dissolution test:** The development of dissolution methods for FDTs is comparable to 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 FDT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for FDT much in the same way as their ordinary tablet counterparts. It has been suggested that USP

2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used.

**10. Stability testing of drug (temperature dependent stability studies):** The fast disintegrating tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(1) 40 ± 1 °C

(2) 50 ± 1°c

(3) 37 ±1 ° C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

**11. Packaging:** Packing is one of the important aspects in manufacturing FDT. The products obtained by various technologies vary in some of the parameters especially in mechanical strength to a good extent. The products obtained by lyophilization process including various technologies such as Zydis, Lyoc, Quicksolv, and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture, and may degrade at higher humidity conditions. For the above reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Paksolv is a special packaging unit, which has a dome-shaped blister, which prevents vertical movement of tablet within the depression and protect tablets from breaking during storage and transport, which is used for Orasolv tablet. Some of the products obtained from Durasolv. WOW Tab, Pharmaburst oraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles *[30, 31]*.

**Table 2: List of patented technology & drug used.**

| Sr. no. | Patented Technology | Process involved | Patent owner | Drugs Used (Brand name) |
|---|---|---|---|---|
| 1 | Zydis | Lyophilization | R.P.Scherer Inc. | Loratidine (Claritin Reditab and Dimetapp Quick Dissolve) |
| 2 | Quicksolv | Lyophilization | Jansen Pharmaceutical | Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-tab) |
| 3 | Flashtab | Lyophilization | Ethypharm | Ibuprofen (Nurofen Flashtab) |
| 4 | Lyoc | Multiparticulate Compressed tablets | Farmlyoc | Phloroglucinol Hydrate (Spasfon Lyoc) |
| 5 | Orasolv | Compressed Tablets | Cima Labs Inc. | Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt) |
| 6 | Durasolv | Molding | Cima Labs Inc. | Hyoscyamine Sulfate (NuLev), Zolmitriptan (ZMT) |
| 7 | Rapitab | Compressed Tablets | Schwarz Pharma | - |
| 8. | Wow tab | Compressed Molded Tablets | Yamanouchi Pharma | Famotidine (Gaster D) |
| 9 | Fast melt | Molding | Yamanouchi Pharma Technologies, Inc. | - |
| 10 | Ziplets | Molding | Élan Corp. | Ibuprofen (Cibalgina Due Fast) |
| 11 | Flashdose | Cotton candy process | Eurand | Tramadol HCl (Relivia Flash dose) |
| 12 | Oraquick | Micromask taste Masking | Fuisz Technology Ltd | Hyoscyamine Sulfate ODT |
| 13 | Advatab | Microcaps & diffuscap CR Technology | KV Pharm. Co., Inc. Eurand International | AdvaTab cetrizine, AdvaTab Paracetamol |

**A promising future**

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. The tablet is the most widely utilised oral dose format. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is the ODT. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds. A number of ODT are commercially available for human use using technologies developed by pharmaceutical companies such as Cardinal Healthcare, Jannsen Pharmaceutical, Bioavail, and Eurand, Yamanouchi. However, these technologies use either expensive processing technology producing fragile tablets that require costly specialised packaging or use conventional tableting procedures which give longer than desired disintegration & still require

specialised packaging. Dr Zeibun Ramtoola and her team at the Royal College of Surgeons in Ireland have addressed the above shortcomings by developing a novel, cost effective one step ODT manufacturing process using conventional tableting technology for the production of robust tablets suitable for conventional packaging. *[33, 34]*

This proprietary technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. "supergenerics" for veterinary or human application. The oral drug delivery market was estimated to be worth $35bn in 2006 & forecast to reach $52bn by 2010 with a CAGR of 10%. Of this, the ODT, taste masked & micro emulsion formulation segments constitute a 22% share with an expected CAGR of 17% to 2010. There is a clear opportunity for new enhanced oral products arising within this market segment. ODT technologies entered the market in the 1980s, they have grown steadily in demand and importance, and their product pipeline is rapidly expanding. In 2004, ODT products generated revenues of well over $2 billion, an increase of 20% over 2003, according to a 2005 report by Technology Catalysts International. With multiple new consumer health and prescription product launches in recent years, the ODT market was predicted to easily reach $3 billion in 2006, including brands and generics. The market continues to grow 20% each year, with a growing penetration of generic ODTs *[35, 36, and 37]*.

**Conclusion**

Fast dissolving tablets constitute an innovative dosage form, which overcomes the problem of swallowing and provides a quick onset of action. The paediatric and geriatric populations are the primary. Targets, as both the groups found it difficult to swallow conventional tablets. 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.

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