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FAST DISSOLVING TABLETS: METHOD AND TECHNOLOGY REVIEW

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ABSTRACT:
In the recent years, many of the pharmaceutical groups are focusing their research work on fast dissolving tablets. Fast dissolving tablets are an innovative drug delivery system in which the consumption of the dosage form without any use of water in taking. So, now-a-days, most of the pharmaceutical companies adopted various technologies to manufacture fast dissolving oral formulation in large scale despite of several limitations as an alternative to traditional over-the-counter medicine forms such as tablets, capsules etc. The main advantage of this technology is the administration to paediatrics and geriatrics patient population where the difficulty of swallowing larger oral dosage forms is eliminated. The basic approach used in development of FDT is the use of superdisintegrants like Cross linked carboxymelhylcellulose (croscarmellose), primogel, polyvinylpyrrolidone (polyplasdone) etc or maximizing pore structure in the formulation. The review describes the various methods and technologies employed in this research area.

Keywords: Fast Dissolving Tablets, Superdisintegrants, Technology

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INTRODUCTION

Recent developments in the technology have presented viable dosage alternatives from oral route for paediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration. Various bio adhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery. The most popular solid dosage forms are being tablets and capsules. The conventional tablet seems to be most popular because of its ease of transportability and comparatively low manufacturing cost but poor patient compliance in case of paediatrics and geriatrics patients because of hand tremors and dysphasia that experienced difficulties in swallowing. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis.

To overcome these problems, scientists have developed innovative drug delivery system known as fast dissolving tablets (FDTs). These are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds[1].

Overview of Oral Mucosa

Drug delivery via the oral mucosa is a promising route. The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. Drugs absorbed via the buccal mucosa enter the systemic circulation directly through the jugular vein. Thus, there is a growing interest in developing alternative dosage forms, i.e. orally fast dissolving tablets, which allow a rapidly dissolving drug[2].

Biopharmaceutical Consideration

When new drug delivery system is discovered, it is necessary that it should compile with biopharmaceutical factors like absorption, distribution, metabolism and excretion.

Pharmacokinetics

In this regard, study has focused on absorption, distribution, metabolism and excretion. After absorption of drug, it attains therapeutic level and then elicits pharmacological effect. Hence, rate and extend of drug absorption are important factors. 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 gets started from mouth, pharynx and oesophagus. 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 (V_d) 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[3].

Pharmacodynamics

- Drug receptor interaction impaired in elderly as well as in young adult due to undevelopment of an organ.
- Decreased ability of the body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- Decreased sensitivity of the CVS to β-adrenergic agonist and antagonist. Immunity is less and taken into consideration while administered antibiotics.
- Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.
- Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed[4].

Challenges in formulating FDTs

Major challenges associated with FDTs are list below.[3, 4]

Palatability

Most orally disintegrating drug delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

Mechanical strength

In order to allow FDTs to disintegrate in the mouth, they are made with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may increase the cost.

Hygroscopicity

Several FDTs 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.

Amount of Drug

For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs.

Aqueous Solubility

Water-soluble drugs 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.

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.

Criteria for Fast Dissolving Tablets

Fast Dissolving Tablets[5]

- Should not require water to swallow.
- Should give a pleasing mouth feel after administration of tablet.
- Should have an acceptable taste masking property.
- Should be harder and less friable.
- Should leave minimal or no residue in mouth after administration.
- Should exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablet using conventional processing and packaging equipments.

Ideal Drug Candidates of Fast Dissolving Tablets[6]

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

INGREDIENTS REQUIRED

While formulating fast dissolving tablets, various ingredients are required like therapeutic drug, Superdisintegrants, diluents and flavouring agents etc. Some of them are listed in Table 1.

Table 1: Ingredients to be used in FDTs[7, 8]

Drug(s)	Ingredients Used	Technologies used	Disintegration Time(sec)
Granisetron HCl	Cyclodextrin, CCS, Magnesium stearate, Lactose, Mannitol.	Direct compression	17.1
Aceclofenac	SSG, Mannitol, MCC.	Direct compression	12.2 - 27.5
Resperidone	Mannitol, Aspartame, PEG400 & 4000, MCC (Ph 200), Gelucire 44/14.	Spray drying and compression	Below 30
Clarithr-omycin or Cefixime	Carrageenan NF, Tricalcium phosphate, Avicel PH 105, LS HPC, Sucrose stearate.	Extrusion Spheronization	Less than 60
Famotidine	Mannitol, PVP K30, Dextran, Sucralose, Sugar, Lactose.	Freeze drying	2-6
Ondansetron	SSG, Polacrillin potassium, MCC, Colloidal SiO2, Aspartame, Talc.	Direct Compression	10-15sec
Ascorbic acid, Cimetidine	Erythritol, D-mannitol, MCC,Corn starch, Pregelatinized starch.	Molding	31-37
Sildenafil	Crosspovidone, Aspartame, Mannitol.	Freeze drying	< 30

#HPMC-Hydroxypropylmethyl Cellulose
#MCC- Microcrystalline cellulose
#CCS –Crosscarmillose sodium
#SSG- Sodium Starch Glycolate
#PEG- Polyethylene glycol
#LS HPC-Low-substituted hydroxyl propyl cellulose
#PVP-Poly vinyl pyrollidone
#EC- Ethyl cellulose

Other ingredients used in FDT

There are some water soluble ingredients which are used in fast dissolving tablets such as: Compressible sugars, binders, surfactants and flavouring agents etc.

METHODS FOR PREPARATION OF FAST DISSOLVING TABLETS

Many methods have been reported for the formulation of Fast dissolving tablets.

Freeze Drying / Lyophilisation

The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is prepared 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 (Figure 1**)**. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze- drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped[9].

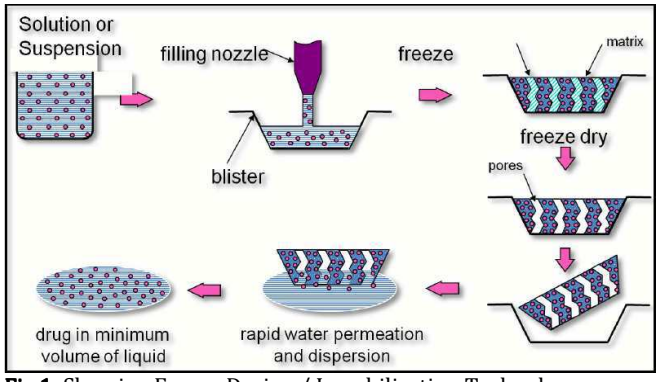

Fig.1: Showing Freeze Drying / Lyophilisation Technology

Tablet Molding

Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. 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 30^0C[10].

Spray Drying

To prepare FDTs, hydrolyzed and non-hydrolyzed gelatine were used as supporting matrix, mannitol as bulking agent and sodium starch glycolate or cross carmellose sodium as Superdisintegrants. Disintegration and dissolution were further increased by adding acidic substances like citric acid or alkali substance like sodium bicarbonate[11].

Sublimation

In this method a subliming material like camphor is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor (Fig.2).

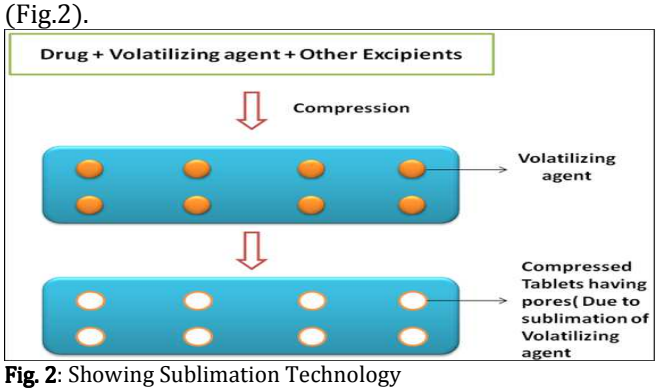

Fig. 2: Showing Sublimation Technology

These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva[12].

Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipient especially Superdisintegrants and sugar based excipient[13].

- **Superdisintegrants**
  In many orally disintegrating tablet technologies based on direct compression, the addition of Super-disintegrants principally affects the rate of disintegration and hence the dissolution.

Table 2: List of Superdisintegrants

Superdisintegrants	Example
Crosscarmellose (Ac-Di-Sol)	Crosslinked Cellulose
Crosspovidone M (Kollidon)	Crosslinked PVP
Sodium starch glycolate (Primogel)	Crosslinked Starch
Soy polysaccharides (Emcosoy)	Natural super Disintegrant
Alginic acid NF (Satialgine)	Crosslinked alginic acid

- **Sugar Based Excipient:** The use of sugar based excipient especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness and hence impart taste masking property and a pleasing mouth feel.

Mass Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets[14].

Nanonization

The nano crystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. This technique is especially advantageous for poor water soluble drugs[15].

Taste Masking

Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers. Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g., Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and complete dissolution in a short period[16].

Cotton Candy

Cotton candy process employed for the formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipient and subsequently compressed to ODT[17].

Three-Dimensional Printing (3DP)

In this, a loose powder is fabricated using the three dimensional printing (3DP) process to formulate a novel fast dissolving drug delivery device (FDDD). FDDD containing the drug acetaminophen were prepared automatically by 3DP system but it is based on computer-aided design models. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG[18].

Fast Dissolving Film

In this, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyl ethyl cellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients are used to form a film after evaporation of solvent[18, 19].

IMPORTANT PATENTED TECHNOLOGY FOR FAST DISSOLVING TABLETS

Zydis Technology

A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatine. The product is very lightweight and fragile, and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds[11].

Orasolv Technology

Orasolv technology has been developed by "CIMA" labs. This technology involves taste masking of active drug. Effervescent disintegrating agent is also used. Conventional blenders and tablet equipments are used for preparation of tablets. Less force of compaction is used for manufacturing to obtain soft and quickly disintegrating tablets[11].

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity[12].

Flash Dose Technology
This technology is patented by Fuisz. Flash dose tablets consist of self-binding shear form matrix termed as floss. Shear form matrices are prepared by flash heat processing[12].

Flashtab Technology
Flashtab technology is patented by Prographarm laboratories. Drug micro granules may be prepared by using conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The micro crystals of micro-granules of the active ingredient are added to the granulated mixture of excipient prepared by wet or dry granulation, and compressed into tablets[13].

Wowtab Technology
Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". In this process, combination of low mouldability saccharides and high mouldability saccharides are used to obtain a rapidly melting strong tablet[14].

Lyoc Technology
This technology is patented by Laboratories L. Lafon, Maisons Alfort, France. In this, freeze drying process is employed but it differ from Zydis in the way that product is frozen on the freeze dryer shelves. During this process, in homogeneity is prevented by sedimentation[15].

Oraquick Technology
A patented taste masking technology is used in the formulation of OraQuick fast-dissolving/disintegrating tablet. KV Pharmaceutical claimed MicroMask as a microsphere technology. As taste masking process does not utilize solvents of any kind and therefore leads to faster and more efficient production of tablets. OraQuick is more appropriate for heat-sensitive drugs due to lower heat of production than alternative fast dissolving/ disintegrating technologies[16].

Shearform Technology
In this technology, a shearform matrix named as 'Floss' is prepared. In this process, sugar is simultaneously subjected to centrifugal force and a temperature gradient is maintained. Due to this, the temperature of the mass get rises and hence an internal flow condition is created which permit a part of it to move with respect of mass. The flowing mass comes out through the spinning head that flings the floss.
It is chopped and recrystallised to provide a uniform flow, which in turn facilitate blending. Then this recrystallised matrix, active drug and other excipient are blended together and finally subjected to compression to form tablets[3, 20].

Ceform Technology
Microspheres of the active drug are prepared in this technology. Drug material alone or in combination with other pharmaceutical substances and excipient is placed into a precision engineered rapidly spinning machine. The centrifugal force throws dry drug blend at high speed through small heated openings. Drug blend goes to liquefy to form a sphere due to heat provided by carefully controlled temperature and drug stability does not get affected. Then microspheres thus formed are subjected to compression to form tablets.[3, 20]

Nanocrystal Technology
The colloidal dispersion of drug and other water-soluble ingredients mixes thoroughly. This mixture is then placed in blister pockets and freeze dried. It is considered that this technology reduces the particle size, which is beneficial to enhance the dissolution, hence bioavailability[3, 21].

Pharmabrust Technology
Pharmaburst technology is being patented by SPI Pharma. In this process, a dry blend of a drug, flavours, and lubricant is produced and then followed by compression into tablets which can dissolve within 30-40 seconds.[3, 21]

Multiflash
It is a multi-unit tablet, composed of coated micro granules and fast-disintegrating excipient. This multiparticulate tablet disintegrates quickly in the oesophagus after being swallowed with a minimum amount of water.[22]

Frosta Technology
A new technology called Frosta (Akina) was developed for making fast-melting tablet (FMT). In this technology, conventional rotary tablet presses can be used for the production of the tablets and no other special instruments are required. Depending on the size, Frosta tablets can disintegrate in less than 10 s after placing them in the oral cavity for easy swallowing.[23]

Table 3: Patented technologies

Technology	Process Involved	Drug Used
Zydis	Lyophilization	Loratidine
Lyoc	Freeze drying	Phloroglucinol hydrate
Quickslov	Lyophilization	Cisapride, Risperidone
Flashtab	Lyophilization	Ibuprofen
Orasolv	Compressed Tablet	Paracetamol, Zolmitriptan
Wow Tab	Compressed Moulded Tablet	Famotidine
Flashdose	Cotton-candy Process	Tramadol HCL
Durasolv	Direct compression	Zolmitriptane, Baclofen
Oraquick	Micromask Taste Masking	Hyoscamine Sulphate
Ziplets	Direct compression	Ibuprofen

COUNSELING POINTS FOR FDTs

Pharmacists are in the ideal position to become familiar with the different technologies and educate their patients on what to expect upon taking their first dose. Clarification from the pharmacist can avoid any confusion or misunderstanding. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly, patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations. Pharmacists may wish to stress the difference between the use of quick-dissolving and effervescent tablets.

CONCLUSION

Besides delivering drug to the body, a drug delivery system aim to improve patient compliance and convenience, and fast dissolving tablets are no exception. The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the paediatric and elderly patient, which constitutes a large proportion of the world's population. The future potential for these products is promising because of the availability of new technologies combined with strong market acceptance and patient demand.

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