INTRODUCTION

1.1 FAST DISSOLVING TABLET

The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular solid dosage forms are tablet and capsule. One drawback of these dosage forms however is the difficulty to swallow. Dysphasia or difficulty in swallowing is seen nearly 35% in the general population. This disorder is also associated with number of medical conditions including stroke, Parkinson’s disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy.\(^1-3\)

Many elderly persons will have difficulties in taking conventional solid dosage form (tablets and capsules) because of their hand tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular system. Other groups, who may experience problems in swallowing solid dosage form, are the mentally ill, the developmentally disabled, uncooperative patients and reduced liquid intake plans or nausea. In some cases such as motion sickness, sudden episode of allergic attack or coughing and an unavailability of water, swallowing of tablets may become difficult.\(^4\)

To fulfill these medical needs, the pharmaceutical technologist have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast Dissolving Tablet (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of water. The fast dissolving tablets usually dissolve in oral cavity within 15 to 60 s. The faster the drug goes into solution, the quicker the absorption and onset of clinical effects. The development of fast dissolving tablets also provides line extension in the market place.\(^1-4\)

1.1.1 Definition

USFDA defines FDT as ‘A solid dosage form containing medicinal substance or active ingredient which disintegrates and dissolves rapidly usually within a matter of seconds when placed upon the tongue’ the disintegration time ranging from several seconds to about a minute.
1.1.2 Advantages of Fast Dissolving Tablets

- Having good mouths feel property.
- Ease administration to patients who refuse to swallow a tablet, such as pediatric, geriatric and psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- Rapid dissolution of drug and absorption, which may give rapid onset of action.
- No need of water to swallow the dosage forms, which is highly convenient during traveling.
- Drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such case bioavailability of drugs is increased.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- Free of the risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.\(^5\)-\(^8\)

1.1.3 Technologies Used to Manufacture Fast Dissolving Tablet

1. **Zydis technology:** R.P. Scherer has patented the zydis technology. Zydis, the best known of the fast-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A zydis tablet is produce by lyophilizing or freeze-drying the drug in a matrix usually consists of gelatin. The product is very light weight and fragile and must be dispensed in a special blister packaging. The zydis product is made to dissolve on the tongue in 2 to 3 s. The zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. The zydis formulation utilizes flavors and sweeteners to optimize the taste of the dosage form. In addition, it utilized micro-encapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter taste of drug.\(^9\),\(^10\)

2. **Orasolv technology:** It is introduced by CIMA Lab’s. In this technology tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Orasolv technology is an example of slightly effervescent tablet
that rapidly dissolves in mouth. In this system, active medicament is taste masked and dispersed in saliva due to the action of effervescent disintegrating agent. Concentration of effervescent mixture usually employed is 20-25% w/w of tablet weight. The tablets produced are soft and friable and packaged in specially designed pick and place packaging.

3. **Durasolv technology:** Durasolv is CIMA Lab’s second-generation fast-dissolving/disintegrating tablet formulation technique which produced in a similar way like orasolv. Durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. The durasolv product is thus produced in a faster and more cost-effective manner. Durasolv is so durable that it can be packaged in either traditional blister packaging or glass vials. One disadvantage of durasolv is that the technology is not compatible with larger doses of active ingredients, because the formulations is subjected to such high pressures on compaction.

4. **Wowtab technology:** Wowtab technology is patented by Yamanouchi Pharmaceutical Co. ‘WOW’ means ‘without water’. The active ingredients may constitute upto 50% w/w of the tablet. In this technology, saccharides of both low and high mouldability are used to prepare the granules. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldability saccharides and then compressed into tablet. The wow tab product dissolves quickly in 15 s or less. Wowtab product can be pack in both into conventional vials and blister packs.

5. **Flashtab technology:** Prographarm laboratories had patented the flashtab technology. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types (disintegrating & swelling agent). Disintegrating agents include reticulated polyvinylpyrrolidine or carboxy methylcellulose. Swelling agents include carboxymethylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. These tablets disintegrate within a one minute in oral cavity.

6. **Flashdose technology:** Flashdose technology has been patented by Fuisz corporation. Flash dose tablets consist of self-binding shearform matrix termed as "floss". The
flash dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure of sugar much like cotton candy. The active drug is also incorporated in crystalline sugar and be compressed into a tablet. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. 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.\textsuperscript{2,14}

1.1.3.2 Conventional Techniques

1. \textbf{Lyophilization or freeze drying:} Freeze drying also commonly known as lyophilization. It is a process in which water is sublimated from the product after freezing. It consists of three phases-

- Freezing to bring the material below its eutectic zone.
- Sublimation drying or primary drying to reduce moisture to around 4\% w/w of dry product.
- Desorption or secondary drying to reduce bound moisture to the required final value.

The ideal drug characteristics for this process are relative water insolubility with fine particle size and good aqueous stability in suspension. This technique allows drying of heat sensitive drugs and biologicals at low temperature thereby eliminating adverse thermal effects and can be stored in dry state with relatively new shelf life. Freeze dried forms offer more rapid dissolution time than other solid products because this technique offers highly porous powder with a very high specific surface area.

The use of freeze drying however is strongly limited by time and handling required for processing and the high cost of equipment and processing. Major disadvantage of the final dosage forms include lack of physical resistance in standard blister packs.\textsuperscript{15}

2. \textbf{Cotton candy process:} This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix form is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients subsequently compressed to fast dissolving tablets. This process can accommodate high doses of drug and offers
improved mechanical strength. However, high-process temperature limits the use of this process.\textsuperscript{16}

3. **Direct compression:** Conventional methods in formulating tablets such as dry granulation\textsuperscript{17}, wet granulation\textsuperscript{18} and direct compression have been adapted to produce FDT’s. All of these techniques, easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipment, commonly available excipients and a limited number of processing steps lead this technique to be a preferred one. High doses can also be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Superdisintegrants play a major role in the disintegration and dissolution of fast dissolving tablets made by direct compression. To ensure a high disintegration rate along with good mouth feel, choice of suitable type and an optimal amount of disintegrant is important.

4. **Mass extrusion:** This technique involves softening the active blend using the solvent mixture of water soluble polyethylene glycol using methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blades to form the tablets. The dried cylinder can be used to coat granules of bitter tasting drugs and thereby masking the bitter taste.\textsuperscript{19}

5. **Spray drying:** Highly porous, fine powders are obtained by this method. The fast dissolving tablet formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agents for matrix, mannitol as bulking agent and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Disintegration and dissolution are further improved by adding effervescent components, i.e. citric acid (an acid) and sodium bicarbonate (an alkali). The formulation was spray dried to yield a porous powder. The fast dissolving tablets made from this method disintegrated within a minute.\textsuperscript{20, 21}

6. **Sublimation:** This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor etc. to other excipients and the compression of blend into tablets. Removal of volatile materials by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc. can also be used as pore
forming agents. Fast dissolving tablets with highly porous structure and good mechanical strength have been developed by this method.  

7. **Tablet molding**: Molding process includes moistening, dissolving or dispersing the drug with a solvent then molding the moist mixture into tablets (compression molding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution or suspension at ambient pressure (no vacuum lyophilization), respectively. The molded tablets formed by compression molding are air-dried. As the compression force employed is lower than conventional tablets, the molded tablet results in highly porous structure, which increases the disintegration and dissolution rate of the product. However, to further improve dissolution rate of the product powder mixture should be sieved through very fine screen. As molding process is employed usually with soluble ingredients (saccharides) which offers improved mouth feel and disintegration of tablets.

1.2 **ANTI-EMETIC DRUGS IN FAST DISSOLVING TABLET**

1.2.1 **Emesis**

Emesis is not a disease, but is only indications of altered physiological functions. Vomiting is a forceful action accomplished by a downward contraction of the diaphragm. At the same time, the abdominal muscles tighten against a relaxed stomach with an open sphincter. The contents of the stomach are propelled up and out.

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![Fig.1.1: Pathophysicsology of emesis](image)
1.2.2 Rational of Selecting Anti-emetic Drug for Fast Dissolving Tablet

Retention of the administered anti-emetic oral doses and its subsequent absorption during anti-emetic therapy is critically affected by recurrent emesis, a process coordinated by vomiting centre in lateral reticular formation of the medulla receiving inputs from the chemoreceptor trigger zone and other neural sites. Vomiting induced by chemotherapy, motion sickness, pregnancy, migraine, physiological processes like impaired gastric emptying and other gastric disturbances will also affect drug retention and absorption. Retention of oral dose is therefore, a prerequisite for absorption to prevent emesis. For drug with low bioavailability, partial drug loss by emesis will result in therapeutic failure. Such anti-emetic drug, after oral dosing undergoes extensive gastric and first pass effect. This results in low bioavailability which therefore, will not minimize the rate of vomiting. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as fast dissolving tablets. Fast dissolving tablet of anti-emetic drugs are designed for rapid and complete absorption in the body and for achieve therapeutic success.

![Vomiting Reflex Diagram]

**Fig. 1.2: Drug treatment of nausea and vomiting**
1.2.3 Selected Anti-emetic Drug for Fast Dissolving Tablet

The prochlorperazine maleate and promethazine theoclolate were selected for the research work. Both drugs are specific anti-emetic drugs prescribed in all cases of nausea and vomiting (chemotherapy, motion sickness, pregnancy, migraine, physiological processes like impaired gastric emptying and other gastric disturbances). These drugs are tasteless molecules and have low bioavailability, low dose and lesser side effects than other anti-emetic drugs.

Drug Profile

A. Prochlorperazine Maleate

Chemical Name: 2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10H
 
phenothiazine

Chemical Structure:

![Chemical Structure](image)

Description:

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<th>White crystalline powder</th>
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Category: Antiemetic, Tranquilliser

Solubility: Slightly soluble in water and freely soluble in ethanol and chloroform

Dose: 15 to 30 mg of prochlorperazine daily as an anti-emetic

Partition Coefficient: Log P(octanol/water) 4.9

Bioavailability: 16% (when pure drug in powder form administer orally)

Half Life: 6.8 h
B. Promethazine Theoclote\textsuperscript{26, 28}

*Chemical Name:* $N, N, \alpha$-Trimethyl-10$H$-phenothiazine-10-ethanamine Theoclote

*Chemical Structure:*

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\begin{center}
\includegraphics[width=0.5\textwidth]{promethazine_theoclote结构.png}
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*Description:*

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*Category:* Antiemetic, Antihistaminic

*Solubility:* Practically insoluble in ether; slightly soluble in water; soluble in ethanol and chloroform

*Dose:* 20 to 100 mg of promethazine theoclote daily, as an anti-emetic

*Partition Coefficient:* Log P (octanol/water) 2.9

*Bioavailability:* 60\% (when pure drug in powder form administer orally)

*Half Life:* 10 - 15 h
1.3 POLYMER SELECTED FOR PROPOSED STUDY

A. Croscarmellose Sodium\textsuperscript{29,30}

\textbf{Synonyms:} Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel.

\textbf{Structural formula:} Croscarmellose sodium is a cross linked polymer of carboxymethylcellulose sodium.

\begin{center}
\includegraphics[width=0.5\textwidth]{croscarmellose_structural_formula.png}
\end{center}

\textbf{Empirical formula and molecular weight:} Typical molecular weight is 90000–700000.

\textbf{Category:} Superdisintegrant and dissolution accelerator.

\textbf{Applications in pharmaceutical formulation:} Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes.

\textbf{Description:} Croscarmellose sodium occurs as an odorless, white or grayish-white powder. Bulk Density 0.529 g/cm\textsuperscript{3} and it is insoluble in water but rapidly swells upto 4-8 times its original volume and also insoluble acetone, ethanol and toluene.

\textbf{Stability and storage conditions:} A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30° for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool and dry place.

B. Crospovidone\textsuperscript{31-34}

\textbf{Synonyms:} Crosslinked povidone; Kollidon CL; Polyplasdone XL.

\textbf{Structural formula:}

\begin{center}
\includegraphics[width=0.2\textwidth]{crospovidone_structural_formula.png}
\end{center}

\textbf{Empirical formula and molecular weight:} (C\textsubscript{6}H\textsubscript{9}O\textsubscript{n}) \(n > 1000000\)
**Category:** Superdisintegrant and dissolution aid.

**Applications in pharmaceutical formulation or technology:** Crospovidone is a water insoluble tablet disintegrant and dissolution enhancer used at 2-5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods.

**Description:** Crospovidone occurs as an odorless, white powder. Density is 1.22 g/cm³ and it is insoluble in water and most common organic solvents.

**Stability and storage conditions:** Tablets prepared with crospovidone have good storage properties. Crospovidone is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of crospovidone remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

**C. Sodium Starch Glycolate**

**Synonyms:** Carboxymethyl starch, sodium salt; Explosol; Glycolys.

**Structural formula:**

![Structural formula of Sodium Starch Glycolate](image)

**Category:** Tablet and capsule disintegrant.

**Applications in pharmaceutical formulation:** Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes.

**Description:** Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing granular powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 μm in diameter, with some less-spherical granules ranging from 10–35 μm in diameter. Bulk density is 0.756 g/cm³ and it is sparingly soluble in ethanol; practically insoluble in water.

**Stability and storage conditions:** Sodium starch glycolate is hygroscopic; it should be stored in an airtight container in a cool and dry place.
REFERENCES


