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Review Article

Revolutionary Advancements in Fast Dissolving Tablets: An In-Depth Exploration

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ABSTRACT

A novel drug delivery system plays a pivotal role in enhancing patient adherence to medication regimens. Among these innovative approaches, fast dissolving tablets (FDT's) stand out as a particularly promising option. FDT's offer a range of benefits, including precise dosing, ease of transport, streamlined manufacturing, robust physical and chemical stability, and they serve as an excellent alternative for both paediatric and geriatric patients. The formulation of FDT's harnesses the advantages of both liquid and conventional tablet formulations, while also surpassing the merits of traditional dosage forms. In this comprehensive review, we delve into the advantages and limitations of FDT's, the imperative need for their formulation, key formulation factors, the role of excipients, methodology, and critical evaluation parameters.

INTRODUCTION

Recent advancements in the field of novel drug delivery systems (NDDS) aim to improve the safety and reduce the toxicity of drug molecules. This is achieved by creating convenient dosage forms for administration and enhancing patient compliance. One notable innovation in this regard is the development of fast-dissolving tablets [1,2]. Fast-dissolving drug delivery systems were initially introduced in the late 1970s as an alternative to traditional dosage forms, particularly for pediatric and geriatric patients. Traditional tablets and capsules, which require ingestion with an 8-ounce glass of water, can pose challenges for individuals who have difficulty swallowing solid oral medications. Fast-dissolving tablets are specifically designed to rapidly dissolve or disintegrate in the saliva, typically within less than 60 seconds. These tablets are a suitable solution for patients facing such difficulties.

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Fast-dissolving/disintegrating tablets (FDDTs) go by various names, including fast-melting, fast-dispersing, rapid-dissolve, rapid-melt, and quick-disintegrating tablets. All FDDTs that have received approval from the Food and Drug Administration (FDA) are categorized as orally disintegrating tablets. Notably, the European Pharmacopoeia has adopted the term "Orodispersible Tablet" to refer to tablets placed in the oral cavity, where they rapidly disperse before being swallowed. The FDDT formulation offers a significant advantage by amalgamating the benefits of both liquid and traditional tablet formulations while surpassing conventional dosage forms. This innovation delivers the convenience of a tablet, coupled with the ease of swallowing typically associated with liquids. FDDTs also excel in providing precise dosing accuracy, outshining primary alternatives such as oral liquids [3].

The oral route of drug administration stands as the most widely accepted method, owing to its self-medication convenience, compactness, ease of production, simple administration, precise dosing, safety, and cost-effectiveness [4-6]. Health care providers bear the responsibility of administering bitter drugs orally, especially when dealing with pediatric and geriatric patients, necessitating an acceptable level of palatability [7].

The most apparent drawback of commonly used oral dosage forms like tablets and capsules is the challenge of swallowing, particularly for pediatric and geriatric patients [5]. To address these medical requirements, pharmaceutical technologists have introduced a novel class of oral dosage forms known as orally disintegrating tablets (ODTs), fast-disintegrating tablets (FDTs), mouth-melting tablets (MMTs), or mouth-dissolving tablets (MDTs). These tablets rapidly disintegrate in saliva, usually within seconds, eliminating the need for water. This results in enhanced drug dissolution, absorption, quicker onset of clinical effects, and increased drug bioavailability compared to conventional dosage forms [8,9]. When these tablets are placed in the oral cavity, saliva quickly infiltrates the pores, leading to rapid tablet disintegration [10].

Recent market studies reveal that more than half of the patient population prefers FDTs over other dosage forms. Mouth-dissolving tablets are primarily formulated using two techniques. The first method involves using superdisintegrants such as croscarmellose sodium, sodium starch glycolate, and crosspovidone. The alternative approach focuses on maximizing the tablet's pore structure through freeze-drying and vacuum drying [8,9].

The absorption of certain drugs can be enhanced through oral cavity absorption and the pregastric absorption of saliva containing dispersed drugs that subsequently enter the stomach. This also results in a reduced amount of the drug being subjected to first-pass metabolism compared to standard tablets [11, 12].

Drug delivery systems (DDS) play a pivotal role in expanding markets, prolonging product life cycles, and creating opportunities. Among these systems, oral administration stands out as the most widely adopted method for achieving systemic effects due to its simplicity of consumption, pain avoidance, versatility, and, most importantly, patient adherence. Solid oral delivery systems offer the advantage of not requiring sterile conditions, thus reducing manufacturing costs. Tablets, with their advantages of patient compliance, precise dosing, and manufacturing efficiency, remain the preferred solid dosage form. Changes in solid dosage form technologies in response to evolving drug discovery, such as genomics, could significantly impact the choice of excipients and equipment [13-16].

Injections are generally less favored by patients, unless facilitated by advanced auto-injectors. Inhalation presents an alternative method for drug

delivery; however, current research on biopharmaceuticals has primarily yielded chemical entities with low molecular weights. The development of fast-dissolving tablets for enhanced oral protein delivery holds great promise for delivering high molecular weight proteins and peptides. Nevertheless, the oral route remains the ideal choice for administering therapeutic agents due to its cost-effectiveness, ease of administration, and resulting high levels of patient compliance [17-20].

Benefits of FDTS [21-22]

Facilitating Administration for Challenging Patients:

- Ease of Administration for Special Populations: Fast Dissolving Tablets (FDTs) offer a practical solution for geriatric, pediatric, mentally disabled, and bed-ridden patients who struggle with swallowing traditional tablets.
- Waterless Consumption: FDTs eliminate the need for water during ingestion, making them particularly advantageous for patients on the go or those with limited access to water. This convenience promotes better patient adherence to treatment.
- Precise Dosing and Portability: These unit solid dosage forms ensure accurate dosing, easy portability, and stable physical and chemical properties, rendering them an ideal option for both pediatric and geriatric patients.
- Enhanced Drug Bioavailability: FDTs enhance bioavailability by facilitating drug absorption through the mouth, pharynx, and esophagus. This pre-gastric absorption can lead to improved clinical performance and reduced adverse effects due to lower dosages.
- Swift Onset of Action: The rapid disintegration, dissolution, and absorption of FDTs in the oral cavity result in a quicker therapeutic response, which can be especially beneficial for patients requiring rapid relief.
- Palatable Taste for All Ages: Taste-masking techniques employed in FDTs create a pleasant experience, notably for pediatric patients, as they effectively mask the bitter taste of medications.
- Enhanced Safety: FDTs reduce the risk of airway obstruction during swallowing, enhancing safety and compliance during administration.
- Prompt Treatment: FDTs allow for rapid drug therapy intervention.
- Cost-Effective Manufacturing: Traditional processing and packaging equipment can be utilized for cost-effective FDT production.
- Simplified Packaging: FDTs can be easily packaged in push-through blisters, eliminating the need for specialized packaging.
- Expanding Business Opportunities: FDTs present new avenues for business growth, including product differentiation, patent extension, uniqueness, line extension, and life-cycle management, offering exclusive opportunities for product promotion.

Restrictions on FDT [23-26]

- Formulating drugs with relatively large doses into Fast Dissolving Tablets (FDTs) poses challenges.
- Patients concurrently taking anti-cholinergic medications may not be ideal candidates for FDTs due to these difficulties.
- Tablets typically lack sufficient mechanical strength, necessitating careful packaging and handling to prevent breakage.
- Improper formulation of tablets can result in an unpleasant taste or gritty sensation in the mouth.
- Furthermore, tablets are more prone to degradation when exposed to humidity and temperature variations.
- FDTs are hygroscopic by nature and must be stored in dry conditions to maintain their integrity.

- In some cases, FDTs may have an impact on the sensation in the mouth.
- Additionally, developing Multi-Unit Dosage Forms (MDTs) for drugs that are challenging to formulate into FDTs is a specialized process requiring specific packaging for stability and product safety.
- It's important to note that drugs with relatively large doses, short half-lives, frequent dosing requirements, or the need for controlled or sustained release are generally unsuitable candidates for FDTs.

The Importance of Advancing Fast-Dissolving Tablet Technology [27]

Patient Considerations: Fast-disintegrating dosage forms offer a practical alternative for individuals who encounter challenges when ingesting conventional tablets and capsules along with an 8-ounce glass of water. This group includes:

- Geriatric Patients: Especially those grappling with conditions like hand tremors and dysphagia.
- Pediatric Patients: Particularly those whose central nervous system and internal muscles are not fully developed, making swallowing difficult.
- Travelers: Individuals experiencing motion sickness or diarrhea while lacking easy access to water.

Effectiveness Emphasis: These formulations primarily emphasize increased bioavailability and quicker onset of action. Notably, some formulations exhibit pre-gastric absorption through saliva dispersion within the oral cavity, especially in cases where the drug dissolves rapidly. This absorption occurs in various regions, including the buccal, pharyngeal, and gastric areas, and proves advantageous for drugs subject to hepatic metabolism, bypassing first-pass metabolism. Moreover, these formulations can enhance safety profiles for drugs that generate substantial amounts of toxic metabolites due to first-pass liver and gastric metabolism. Additionally, they benefit drugs with a significant fraction of absorption occurring in the oral cavity and pre-gastric segments of the gastrointestinal tract.

DEVELOPMENT

Obstacles Encountered in Developing Fast-Dissolving Tablets (FDTs)

Mechanical Strength and Disintegration Time: Increasing the mechanical strength inevitably leads to a prolongation of the disintegration time. Striking the right balance between these two factors remains crucial. Fast-dissolving tablets (FDTs) are meticulously crafted to achieve disintegration times typically under a minute. However, the challenge lies in simultaneously maintaining robust mechanical integrity [28].

Taste Masking: Given that the majority of drugs possess unappealing flavors, rapid disintegrating drug delivery systems often incorporate the medication in a taste-concealed form. These delivery systems disintegrate or dissolve in the patient's oral cavity, liberating the active ingredients to interact with the taste buds. Consequently, the art of taste-masking becomes pivotal for patient compliance [29,30].

Aqueous Solubility: Water-soluble drugs present a myriad of formulation challenges because they tend to form eutectic mixtures, leading to freezing-point depression and the formation of a glassy solid that may collapse during drying due to a loss of structural support during the sublimation process. To combat this, various matrix-forming excipients, such as mannitol, are employed to induce crystallinity and provide rigidity to the amorphous composite [31,32].

Hygroscopicity: Hygroscopicity is a critical characteristic of powders, especially for fairly soluble compounds, where it is closely tied to their solubility. FDTs must exhibit low sensitivity to humidity, a challenge heightened by the use of

highly water-soluble excipients aimed at enhancing fast-dissolving properties and mouthfeel. Some of these excipients are highly susceptible to moisture, with a propensity to deliquesce in high humidity conditions. Effective packaging or other protective strategies are essential to shield FDTs from various environmental factors [33-35].

Amount of Drug: The capacity to incorporate drug into each unit dose significantly limits the application of FDT technologies. For lyophilized dosage forms, drug doses must remain below 400 mg for insoluble drugs and under 60 mg for soluble drugs. This parameter becomes especially daunting when formulating fast-dissolving oral films or wafers [36].

Size of Tablet: Studies indicate that the most easily swallowed tablets measure 7-8 mm, while those easiest to handle are larger than 8 mm. Thus, achieving a tablet size that is both easy to ingest and handle presents a formidable challenge [37].

Mouth Feel: FDTs should not disintegrate into large particles within the oral cavity. The post-disintegration particles should be as minuscule as possible. Additionally, the incorporation of flavors and cooling agents like menthol can enhance the overall mouthfeel [38].

Sensitivity to Environmental Conditions: Maintaining low sensitivity to environmental conditions, such as humidity and temperature, is imperative for FDTs. This is especially critical since most materials used in FDTs are designed to dissolve with minimal water involvement [38].

CRITERIA FOR EXCIPIENT USED IN FORMULATION OF FDTs [39-41]

- Rapid disintegration is a prerequisite.
- The individual characteristics must remain non-intrusive to the ODTs.
- It must not engage with the drug or other additives.
- It should not compromise the effectiveness and sensory qualities of the product.
- When selecting a binder, whether singular or a combination, utmost care must be exercised to ensure the final product's integrity and stability.
- The excipients' melting point should fall within the 30-35ºC range.
- The binder can exist in liquid, semi-solid, solid, or polymeric forms.

EXCIPIENTS USED IN FDT's PREPARATION

Excipients used in FDTs contain at least one super disintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavourings.

Table 1: Name and weight percentage of various excipients [42]

Name of the Excipients	% used
Super disintegrants	1-15%
Binders	5-10%
Antistatic agent	0-10%
Diluents	0-85%

SUPER DISINTEGRANTS

As the days go by, there is a growing demand for faster-disintegrating formulations. Consequently, pharmacists must develop disintegrants, specifically Super disintegrants, that operate effectively at lower concentrations and possess superior disintegration capabilities. These Super disintegrants exhibit enhanced intragranular effectiveness, primarily through a mechanism involving swelling. The swelling exerts pressure outward or radially, leading to the tablet bursting or a rapid absorption of water. This results in a significant expansion in the granule volume, thereby facilitating the disintegration process [43-45].

Here are some factors to take into account when selecting super disintegrants:

Disintegration: The disintegrant needs to rapidly absorb saliva within the tablet to induce volume expansion and hydrostatic pressure, facilitating swift disintegration in the mouth.

Compactibility: It is advantageous to achieve Orodispersible Tablets (ODTs) with desirable hardness and reduced friability under a specific compression force. This ensures the creation of robust tablets, eliminating the necessity for specialized packaging and maximizing production efficiency.

Mouth Feel: The presence of large particles can lead to an unpleasant gritty sensation in the mouth. Hence, smaller particles are preferable. However, if the tablet acquires a gel-like consistency upon contact with water, it may result in an objectionable gummy texture for many consumers.

Flow: In conventional tablet formulations, super disintegrants are typically employed at levels ranging from 2% to 5% of the tablet composition. However, when formulating ODTs, the disintegrant concentration can be considerably higher [46].

Table 2: List of Superdisintegrants [47]

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 and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Cross linked 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 nutritional Products
Calcium silicate		-Wicking Action	Highly porous, Optimum concentration is b/ 20-40%

BULKING MATERIALS

Bulking materials play a pivotal role in the creation of rapidly dissolving tablets. These substances serve multiple functions, acting as diluents, fillers, and cost-effective components. Bulking agents not only enhance the tablet's texture, leading to quicker disintegration in the mouth, but they also reduce the concentration of the active ingredient within the formulation. For this type of drug delivery system, it is advisable to employ bulking agents that are primarily sugar-based. Examples include mannitol, polydextrose, lactitol, DCL (direct compressible lactose), and starch hydrolysate. Sugar-based bulking agents are preferred due to their higher aqueous solubility and positive impact on sensory perception. Mannitol, in particular, stands out for its remarkable aqueous solubility and sensory attributes. In practice, bulking agents are incorporated into the final composition in a range

spanning from 10 percent to approximately 90 percent by weight [48].

LUBRICANTS

While not absolutely necessary, excipients can enhance the palatability of these tablets once they disintegrate in the mouth. Lubricants play a role in eliminating any rough texture and aiding in the smooth transfer of the drug from the mouth to the stomach [49].

TASTE MASKING

Materials used for the purpose of taste-masking are often categorized based on their ability to modify basic tastes. Flavoring and perfuming agents can be derived from natural or synthetic sources. Natural products encompass a variety of items, including fruit juices, aromatic oils like peppermint and lemon oils, herbs, spices, and distilled fractions thereof. These natural substances can be acquired in concentrated extracts, alcoholic or aqueous solutions, syrups, or spirits.

In addition to these traditional materials, several compositions have demonstrated effective taste-masking properties while enhancing flavor. Examples include alkaline earth oxide, alkaline earth hydroxide, or an alkaline hydroxide. Another composition of note involves phosphorylated amino acids like phosphotyrosine, phosphoserine, phosphothreonine, and their combinations. Anethole, for instance, effectively conceals the bitter taste and aftertaste associated with zinc, which is often used in the treatment of the common cold. Clove oil and calcium carbonate have also proven particularly beneficial in masking the unpleasant taste of active ingredients in formulations designed for chewing or dissolving in the mouth prior to ingestion [50-53].

EMULSIFYING AGENT

Emulsifying agents play a crucial role as additives in the development of rapidly dissolving tablets. They facilitate quick disintegration and drug release, eliminating the need for chewing, swallowing, or the consumption of water. Moreover, the inclusion of emulsifying agents is beneficial for stabilizing incompatible mixtures and improving the availability of the drug. A diverse selection of emulsifiers is recommended for formulating fast-dissolving tablets, including substances such as alkyl sulfates, propylene glycol esters, lecithin, sucrose esters, and others. These agents can be introduced within a range spanning from 0.05 percent to approximately 15 percent by weight of the final tablet composition [54].

METHODOLOGY

Strategies for Formulating Rapidly Dissolving Tablets:

Conventional Technologies

Freeze Drying/Lyophilization [55]: Freeze drying is a process that involves removing water from a product after it has been frozen, resulting in freeze-dried forms that dissolve more rapidly than other solid products. The lyophilization process also imparts a glossy, amorphous structure to the bulking agent and sometimes to the drug, which enhances the dissolution characteristics of the formulation.

Tablet Molding: Compression molding is a method used to create tablets from soluble ingredients, such as sugars. This process involves compressing a powder mixture that has been moistened with a solvent, typically ethanol or water, into mold plates to form a wetted mass. Molded tablets have advantages such as rapid disintegration and improved taste due to their water-soluble sugar composition. These properties are further enhanced when tablets with porous structures are produced or when components are physically modified during the molding process. In comparison to lyophilization, tablets produced through molding are more adaptable to industrial-scale production. Both lyophilization and molding techniques result in rapidly disintegrating tablets (RDTs) that dissolve within approximately 30 seconds, but they tend to have low physical

resistance and are highly friable. Conversely, tablets prepared via direct compression are less prone to friability but disintegrate at a slower rate [56, 57].

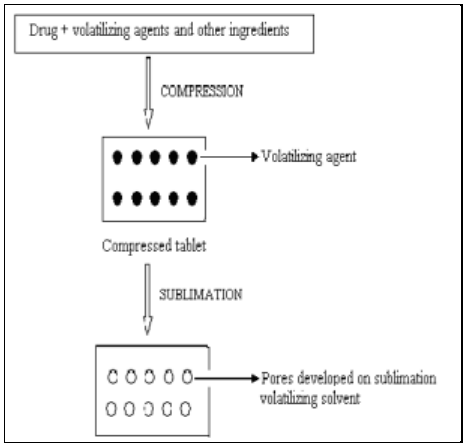
Direct Compression Method: The direct compression method is the simplest and most efficient technique for manufacturing tablets. It is particularly suitable for the preparation of Fast Disintegrating Tablets (FDTs) due to the availability of advanced excipients, especially superdisintegrants and sugar-based excipients.

(a) Superdisintegrants: Tablet disintegration time can be enhanced by increasing the concentration of disintegrants. When the disintegrants are below a critical concentration, tablet disintegration time decreases as the concentration of disintegrants increases. However, once the critical concentration is exceeded, the disintegration time tends to remain constant or even increase. Notably, microcrystalline cellulose, cross-linked carboxymethyl cellulose sodium, cross-linked polyvinyl pyrrolidone, and partially substituted hydroxypropyl cellulose, despite being water-insoluble, have the ability to absorb water and swell due to capillary action. These properties make them effective disintegrants in the formulation of fast-dissolving tablets. Fast tablet disintegration can also be achieved by incorporating effervescent disintegrating agents that release carbon dioxide. This phenomenon not only aids in tablet disintegration but also partially masks the undesirable taste of the drug. However, one significant drawback of effervescent excipients is their hygroscopic nature, requiring strict control of humidity conditions and protection of the final product, thereby affecting the overall production cost [58].

(b) Sugar-Based Excipients: Another method for manufacturing Fast-Dissolving Tablets (FDT) involves direct compression with the use of sugar-based excipients, particularly bulking agents such as dextrose, fructose, isomalt, lactilol, maltitol, sorbitol, starch hydrolysate, polydextrose, and xylitol. These sugar-based excipients exhibit high aqueous solubility and sweetness, making them valuable for imparting taste-masking properties and a pleasant mouthfeel to the tablets [59-61].

Spray Drying: The fabrication of microspheres involved the utilization of spray drying, a prominent technique in pharmaceutical processing. This method is favored for its simplicity, as it entails a single-step process that can be readily managed and scaled up. Spray drying enjoys extensive application within the pharmaceutical and biochemical sectors, with the final particle size being influenced by several factors, including the dimensions of the nozzle employed during processing [62-65].

Sublimation: To create Fast Disintegrating Tablets (FDTs) characterized by high porosity, the sublimation process has been employed. This technique entails the compression of volatile ingredients, along with other excipients, into tablets, ultimately undergoing a sublimation process. Inert solid components possessing high volatility, such as ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene-tetramine, naphthalene, phthalic anhydride, urea, and urethene, have been employed for this purpose. Additionally, solvents like cyclohexane and benzene have been recommended for generating porosity within the matrix [66].



Phase Transition Process: To create Fast Dissolving Tablets (FDTs) without the need for specialized equipment, a critical approach involves the combination of sugar alcohols with varying melting points and the introduction of a phase transition during the manufacturing process. These FDTs are manufactured by compressing a powder blend containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), followed by a 15-minute heating step at approximately 93°C. This heating process results in an increase in the median pore size of the tablets and enhances tablet hardness. Remarkably, the enhancement of tablet hardness due to heating and storage remains consistent, regardless of the crystalline state of the lower melting point sugar alcohol [67].

Melt Extrusion Method: In the melt extrusion method, the drug/carrier mixture is typically processed using a twin-screw extruder. This method involves simultaneously melting and homogenizing the drug/carrier mixture, which is then extruded and shaped into various forms such as tablets, granules, pellets, sheets, sticks, or powder. These intermediates can subsequently undergo further processing to create traditional tablets. One notable advantage of the hot melt extrusion method is that the drug/carrier mixture is exposed to elevated temperatures for only about 1 minute, allowing for the processing of thermally sensitive drugs with relative ease [68].

PATENTED TECHNOLOGIES

Zydis Technology: represents a groundbreaking innovation in the realm of pharmaceuticals, introducing the concept of a rapidly dissolving dosage form. This innovation involves a distinctive freeze-drying process, resulting in a tablet where the active drug is integrated into a water-soluble matrix. This matrix is then converted into blister pockets and subjected to freeze-drying, removing water through sublimation. When Zydis units are placed in the mouth, the freeze-dried structure disintegrates instantly, eliminating the need for water to facilitate swallowing.

The Zydis matrix comprises a blend of materials meticulously selected to achieve specific objectives. Polymers like gelatin, dextran, or alginates are incorporated to enhance structural integrity during handling, resulting in a glossy and amorphous configuration. Mannitol or sorbitol is added to impart crystalline attributes, elegance, and hardness to the formulation. Water plays a crucial role as a medium, ensuring the creation of a porous dosage form. Additionally, collapse protectants such as glycine may be employed to prevent shrinkage of the dosage form during freeze-drying and prolonged storage [69, 70].

Orasolv Technology: developed by Cima Labs, adopts a different approach. It leverages effervescent disintegrating agents that are compressed under low pressure to manufacture Fast Dissolving Tablets (FDTs). During tablet dissolution, the release of carbon dioxide generates a fizzy sensation, enhancing the overall sensory experience. Typically, the effervescent mixture constitutes 20-25% of the tablet's total weight. Due to the low compression force applied during tablet production, these tablets possess a soft and delicate nature. To address this fragility and protect the tablets from damage during storage and transportation, the innovative Paksolv packaging solution was introduced. Paksolv takes the form of a dome-shaped blister package, designed to prevent vertical movement of the tablets within the cavities. This packaging not only offers protection against moisture and light but also incorporates child-resistant features, ensuring the safety and integrity of the tablets [71].

Durasolv Technology: Durasolv represents CIMA labs' patented innovation in pharmaceutical technology. Tablets produced using this cutting-edge method comprise active drugs, fillers, and a lubricant. These tablets are manufactured using

conventional tableting equipment and possess excellent structural integrity. They can be conveniently packaged using conventional blister packaging systems. Durasolv stands out as an ideal choice for products with low concentrations of active ingredients [72, 73].

Wowtab Technology: Wowtab Technology, pioneered by the Yamanauchi pharmaceutical company, derives its name from its unique feature of being "without water." In this method, the active ingredients can make up to 50% of the tablet's weight. The process involves using saccharides with varying degrees of moldability to create granules. Moldability refers to a compound's ability to be compressed, with highly moldable substances exhibiting high compressibility and slower dissolution. To achieve tablets with appropriate hardness, a combination of high and low moldability saccharides is employed. The active ingredients are mixed with low moldability saccharides, granulated with high moldability saccharides, and then compressed into tablets. Wowtab products dissolve rapidly in 15 seconds or less. These products can be packaged in both traditional bottles and blister packs [74].

Flashtab Technology (Ethypharm France): Flashtab Technology, developed by Ethypharm in France, encompasses the granulation of excipients through wet or dry granulation methods, followed by compression into tablets. This method employs two types of excipients: disintegrating agents such as reticulated polyvinylpyrrolidine or carboxymethylcellulose, and swelling agents like carboxymethylcellulose, starch, modified starch, microcrystalline cellulose, and carboxymethylated starch. The resulting tablets exhibit satisfactory physical resistance, and their disintegration time is within 1 minute [75, 76].

Oraquick Technology: The Oraquick rapid dissolving tablet formulation incorporates a patented taste masking technology. KV Pharmaceutical asserts that its Micro Mask microsphere technology surpasses other taste masking alternatives in terms of mouthfeel. This unique taste masking process is solvent-free, resulting in faster and more efficient outcomes. Moreover, Oraquick is particularly suitable for heat-sensitive drugs due to its lower heat production compared to other fast-dissolving/disintegrating technologies [77, 78].

Nanocrystal Technology: Elan's proprietary Nanocrystal technology enhances the formulation and enhances the activity and final characteristics of fast-disintegrating tablets. Reducing particle size increases the surface area, leading to an accelerated dissolution rate. This can be reliably and effectively achieved through Nanocrystal technology. Nanocrystal particles consist of drug substances, typically less than 1000 nanometers (nm) in diameter, produced by employing a proprietary wet milling technique [79].

Frosta Technology (Akina): Frosta Technology employs the concept of formulating plastic granules and compressing them at low pressure to create robust tablets with high porosity. These plastic granules consist of porous and plastic materials, water penetration enhancers, and binders. The process typically involves mixing the porous plastic material with a water penetration enhancer, followed by granulation with a binder. The resulting tablets exhibit excellent hardness and rapid disintegration times, typically ranging from 15 to 30 seconds, depending on the tablet size. It's worth noting that the inclusion of a filler may reduce tablet porosity, leading to a longer disintegration time [80].

EVALUATION

Preformulation Studies Fast Dissolving Tablet

Angle of Repose:

To ascertain the angle of rest, the funnel method was employed. A funnel capable of being placed vertically was positioned on a stand with a height of 6.3 cm. The open end of the funnel remained sealed with a thumb until the drug was introduced.

A quantity of 5 grams of powder was then carefully poured into the funnel, which could be elevated vertically until achieving the maximum cone height denoted as "h." Subsequently, the radius of the resulting heap was measured, and the angle of repose, represented as "θ," was computed using the formula [81-85].

$$Tan\Theta = h/r$$

$$Therefore\ \Theta = Tan^{-1}\ h/r$$

Where Θ = Angle of repose

Bulk Density (Db):

The bulk density is determined by the proportion of the overall powder mass to its bulk volume. This measurement is obtained by pouring powdered material (which has been sifted through a standard sieve #20) into a measuring cylinder and recording the initial weight. This initial volume is referred to as the bulk volume, and the bulk density is subsequently calculated using the formula provided below. It is expressed in g/ml and is given by,

$$Db = M/Vb$$

Where, M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density (Dt):

This refers to the proportion of the entire powder mass in relation to the tapped volume of the powder. The volume was determined by tapping the powder 750 times, and we recorded the tapped volume unless the disparity between these two volumes exceeded 2%. In cases where the difference exceeded 2%, we continued tapping for an additional 1250 times and documented the tapped volume. The tapping process was repeated until the difference between successive volumes remained under 2%, as performed using a bulk density apparatus.

It is expressed in g/ml and is given by,

$$Dt = M / Vt$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

Carr's Index (Or) % Compressibility: It indicates powder flow properties. It is expressed in percentage and is give (Table 3)

$$I = (Dt - Db)/ Dt \times 100$$

Where, Dt is the tapped density of the powder

Db is the bulk density of the powder.

Table 3: Relationship between % compressibility and flow ability [86, 87]

% Compressibility	Flow ability
5-10	Excellent
12-16	Good
18-21	Fair Passable
23-25	Poor
33-38	Very Poor
<40	Very Very Poor

Hausner Ratio [88]: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

Hausner ratio =ñt/ñd

Where, ñt = tapped density

ñd = bulk density. Lower Hausner ratio (1.25).

EVALUATION OF FAST DISSOLVING TABLETS

By Weight Variation: 20 tablets are selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. [100] Table 4. Weight variation specification as per I.P [89, 90].

Table 4: Weight variation specification as per I.P [91, 92]

Average Weight of Tablet	% Deviation
80 mg or less	±10
80 mg to 250 mg	±7.5
250 mg or more	±5

Tablet Hardness [93]: 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 or Pfizer hardness tester.

Uniformity of Weight [94]: I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity dropped in it. Time required for complete dispersion was determined.

Table 5: Uniformity of Weight

Average weight of Tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Accelerated Stability Study [95]: The Orally disintegrating tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1°C
(ii) 50 ± 1°C
(iii) 37±1°C and Relative Humidity= 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.

Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the Purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight [96].

F = Wt initial–Wt final / Wt initial x 100

Wetting Time [97]: Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

dl/dt = r¡cosq/ (4hl)

Where l is the length of penetration,

r is the capillary radius,

¡ is the surface tension,

h is the liquid viscosity, t is the time, and q is the contact angle.

Dissolution Test: The development of dissolution methods for ODTs is comparable with the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for ODT much in the same way as conventional tablets [98].

Thickness Variation: Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer. The mean SD values were calculated [99]. **Disintegration Time:** The test was carried out on 6 tablets using the apparatus specified in I.P.- 1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with

no palatable mass remaining in the apparatus was measured in seconds 28.

Modified Disintegration Test: The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for FDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted [100].

***In-Vitro* Dispersion Time Test:** To determine dispersion time 10 ml measuring cylinder was taken in which 6 ml distilled water was added and tablet was dropped in it. Time required for complete dispersion was determined [101].

Packaging: The products obtained by lyophilization process including various technologies such as Quicksolv, Nanocrystal, Zydis, and Lyoc 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 [102-105].

MARKETED PRODUCTS: [106-110]

Table 6: Marketed product of MDT's

Brand Name	Active ingredient	Application	Company
Claritin® RediTabs®	Loratadine	Antihistamine	Scherig corporation
Feldene Melt®	Piroxicam	NSAID's	Pfizer
Maxalt –MLT	Rizatritpan benzoate	Migraine	Merck
Pepeid® ODT	Femotidene	Anti-ulcer	Merck
Zyperxa®	Olazepine	Psychotropic	Eli Lilly
Zofran® ODT	Olandansetron	Antiemetic	Galaxo Smith kline
Resperdal® M-TabTM	Risperidone	Schizophrenia	Janssen
ZubrinTM(Pet drug)	Tepoxelin	Canine NSAIDs	Scherig corporation
ZelaparTM	Selegiline	Parkinsons disease	ElanlAmarincorporation
Klonopin® wafer	Clonazepam	Sedation	Roche
Childrens Dimetapp® ND	Loratadine	Allergy	Wyeth consumer Healthcare
ImodiumIstant Melts	Loperamide HCL	Antidiarrheal	Janssen
Propulsid® Quicksolv ®	Cisapride Monohydrate	Gastrointestinal Prokinetic Agent	Janssen
Tempra Quicksolv®	Acetaminophen	Analgesic	Bristol-Mters squibb
Remeron® Soltab®	Mirtazapine	Anti-depression	Organon Inc.
Triaminic® Softchews®	Various combination	Paediatric cold cough, Allergy	Novartis consumer Health
Zomig-ZMT® and Rapimelt®	Zolmitriptan	Anti-migraine AstraZeneca	AstraZeneca Alavert® Loratadine Allergy
DuraSolv® Alavert®	Loratadine	Allergy	Wyeth consumer Healthcare

NuLev®	Hyoscyamine sulfate	Anti-ulcer	Schwarz Pharma
Kemstro™	Baclofen	Anti-spastic Analgesic	Schwarz Pharma
Benadryl® Fastmelt®	Diphenhydramine Citrate	Sinus pressure relief	Pfizer
Nasea OD	Ramosetoron HCl	Anti-emetic	Yamanouchi
Gaster D	Famotidine	Anti-ulcer	Yamanouchi
Excedrin® QuickTabs	Acetaminophen	Pain reliever	Bristol-Myers Squibb

Table 7: Formulation challenges of FDT's [111-114]

Challenges	Brief Description
Mechanical strength & disintegration time	MDTs are formulated to get disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. A lot of MDTs are easily broken and there are many chances that such fragile tablet will break during packing, transport or handling by the patients. It is very natural that increasing the mechanical strength will delay the disintegration time
Masking of Taste	Numerous drugs are bitter in taste. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.
The Mouth feel	Tablet should not disintegrate into bigger particles in the oral cavity. The particles generated after disintegration of the Tablet should be as small as possible. Tablet should leave minimal or no residue in mouth after oral administration.
Environmental Sensitivity	Tablet usually should show low sensitivity to environment conditions such as humidity and temperature as most of the materials used in a Tablet are meant to dissolve in minimum quantity of water.
Palatability	As the majority of drugs are unpalatable, tablets should contain the medicament in a tastemasked form
Mechanical strength to withstand sock	In order to allow ODTs to disintegrate in the oral void, they are made of either very porous and soft-molded matrices or compressed into tablets with very little compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost.

CONCLUSION

The Fast-Dissolving Tablet (FDT) concept emerged as a solution to address certain challenges associated with traditional solid dosage forms. These challenges included issues like tablet swallowing difficulties, especially in paediatric and geriatric patients. FDTs have the potential to enhance several aspects of medication delivery, such as efficacy, bioavailability, rapid onset of action, and overall patient compliance. This improvement is primarily attributed to the swift absorption of the medication from the oral cavity into the gastrointestinal tract as saliva naturally passes. In the future, FDTs may become the preferred and frequently prescribed dosage form due to their ability to deliver rapid therapeutic effects, often within a matter of minutes.

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