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Advancing oral drug delivery: The science of fast dissolving tablets (FDTs)

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ABSTRACT

The field of oral drug delivery has witnessed significant advancements, with a focus on developing innovative formulations to address challenges associated with traditional dosage forms, especially for patients with difficulties in swallowing. Fast Dissolving Tablets (FDTs) have emerged as a promising class of tablets designed to rapidly disintegrate or dissolve in saliva, providing a convenient and patient-friendly alternative for various populations.

This article explores the unique properties, advantages, and potential applications of FDTs, emphasizing their role in overcoming challenges posed by conventional oral drug delivery systems. FDTs offer rapid dissolution within 15-120 seconds in the buccal cavity, facilitating direct absorption through the buccal mucosa and ensuring quick therapeutic effects. This characteristic proves particularly beneficial for individuals facing swallowing challenges, such as pediatric and geriatric patients, or those with conditions like dysphagia.

Recognizing the significance of FDTs, the European Pharmacopoeia (EP) has officially recognized them as “oral dissolving tablets," highlighting their acceptance in both academic and industrial settings. The article delves into the anatomical and physiological characteristics of the oral cavity, shedding light on the buccal epithelium, oral mucosa vascularization, and salivary flow, which play crucial roles in drug absorption.

The ideal features of FDTs include rapid dissolution or disintegration, high drug load capacity, masking of bitter taste, positive mouth feel, ease of transport, and reduced sensitivity to environmental factors. The advantages of FDTs extend to their administration for patients unable to swallow, convenient treatment for bedridden and mobile patients, enhanced mouth feel and taste masking, ease of administration, and precise dosing.

Despite their advantages, FDTs come with limitations, including issues related to mechanical strength, hygroscopic nature, brittleness, and challenges with bitter drugs or unpleasant odors. Overcoming these challenges requires a careful formulation approach to balance rapid disintegration with mechanical strength and taste masking.

The article also discusses the salient characteristics of Fast Dissolving Dosage Forms (FDDDS) and various techniques for preparing FDTs, such as freeze-drying, tablet molding, and spray drying. Additionally, it explores the role of non-invasive drug delivery systems in addressing pharmaceutical industry needs, including improving drug half-life, solubility/stability, and bioavailability.

1. Introduction

Oral drug delivery remains a preferred route for its ease of administration, patient acceptance, and the potential to enhance bioavailability, especially for medications undergoing first-pass metabolism.[1] The demand for rapid onset of action and improved bioavailability has driven the development of dosage forms that quickly disintegrate and dissolve in the buccal cavity, facilitating direct absorption through the buccal

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mucosa into the systemic circulation. This approach proves particularly beneficial for individuals facing challenges in swallowing, including pediatric and geriatric patients, as well as those with limited liquid intake or conditions like dysphagia.[2]

The need for innovative formulations arises from the recognition that traditional oral dosage forms, such as capsules and tablets, pose difficulties for certain patient populations. Swallowing-related issues affect approximately 35% of the total population, with dysphagia presenting a significant hurdle in drug delivery and therapeutic efficacy.[3] This challenge is particularly pronounced among children, the elderly, and individuals with neurological or developmental disorders, mental health conditions, or those experiencing nausea or low liquid intake.

Addressing these challenges, scientists have endeavored to create a novel class of tablets known as Fast Dissolving Tablets (FDTs). FDTs are designed to disintegrate or dissolve rapidly in saliva without the need for water, offering a convenient and patient-friendly alternative for those with swallowing difficulties. This innovation holds promise for a wide range of patient groups, including those with motion sickness, sudden allergic reactions, or limited access to water.[4,5] FDTs exhibit the advantage of quick dissolution within 15-120 seconds when placed in the oral cavity, ensuring rapid absorption and therapeutic effect. Some FDTs are specifically formulated to be absorbed via the mucosa of the esophageal and buccal areas, further enhancing bioavailability compared to traditional dosage forms. These tablets have garnered attention not only for their efficacy but also for their potential to address the challenges posed by alternative oral treatments like suspensions, chewing tablets, gums, and effervescent tablets.

Recognizing the significance of FDTs, the European Pharmacopoeia (EP) has officially recognized them as “oral dissolving tablets." This acknowledgment underscores the acceptance of FDTs in both academic and industrial settings. In light of these advancements, this article aims to delve into the unique properties, advantages, and potential applications of Fast Dissolving Tablets, providing insights into their formulation, mechanisms of action, and their role in overcoming challenges associated with conventional oral drug delivery systems.

A critical challenge is formulating FDTs in a way that the unique properties of the drug are not adversely affected during the manufacturing process.[6–8]

The utilization of non-invasive drug delivery systems is on the rise due to several factors, including poor patient compliance and acceptance of current delivery methods, limited market space for drug makers, and the escalating costs associated with disease management.

The current needs of the pharmaceutical industry revolve around addressing various challenges, including enhancing the half-life, solubility/stability, and bioavailability of poorly soluble drugs. Key issues faced by the biopharmaceutical industry include improving safety by reducing gastrointestinal adverse effects, enhancing organ targeting effectiveness, and improving patient compliance through sustained-release dosage forms or formulations that are easy to swallow.[9–12] Innovation and the development of new technologies in drug delivery systems are deemed crucial for the survival and competitiveness of pharmaceutical companies. Marketing also plays a pivotal role in the growth of Fast Dissolving Tablets (FDTs). As a medicinal entity nears the end of its patient's life, pharmaceutical companies are compelled to manufacture an updated and improved product, expanding market exclusivity and providing a more suitable drug or dosage form to the patient group. Fast Dissolving Tablets, similar to sustained-release (SR) dosage forms, contribute to an expansion of market exclusivity, leading to increased sales. Despite the higher manufacturing costs associated with advanced dosage forms, this additional cost is not passed on to the users but is considered an investment in meeting patient needs. For epileptic patients, specific parameters must be considered for optimal patient compliance. Difficulties in swallowing tablets or other dosage forms during unconscious phases.[13,14] Challenges faced by geriatric patients in swallowing traditional tablets. In response to these parameters, the pharmaceutical industry is actively exploring new types of dosage forms for the convenience of patients.[15] Fast-dissolving tablets have gained popularity due to their self-administration capabilities, absence of the need for water, and rapid disintegration and dissolution.

1.1. Anatomical and physiological characteristics of the oral cavity

The buccal cavity, a crucial gateway for drug administration, presents a complex anatomical and physiological landscape. Comprising distinct regions such as the masticatory, lining, and specialized mucosa, each with unique characteristics, the buccal cavity plays a vital role in drug absorption. This comprehensive exploration delves into the intricacies of the buccal epithelium, oral mucosa vascularization, and salivary flow, shedding light on their relevance to Fast Dissolving Tablets (FDTs) and drug delivery systems. Understanding these aspects not only provides insights into the physiological processes but also offers a foundation for optimizing drug formulations and enhancing therapeutic outcomes.[16–18]

1.2. Masticatory mucosa

The masticatory mucosa, with a thickness ranging from 100 to 200 μm, serves a protective role for the gingiva and hard palate. Representing 25% of the oral mucosa, it withstands shear and abrasion stresses during mastication, emphasizing its resilience and durability.[19]

1.3. Lining mucosa

Covering 60% of the overall oral mucosa, the lining mucosa, with a thickness of 500 to 800 μm, is distributed across the cheeks, lips, tongue's lower surface, and the oral cavity surface. Its versatility and coverage make it a significant contributor to the overall mucosal structure.[20]

1.4. Specialized mucosa

Encompassing 15% of the overall mucosa, the specialized mucosa resides on the tongue's dorsum and actively participates in taste sensation. Its specific functions highlight the diverse roles played by different regions within the buccal cavity.[21]

1.5. Buccal epithelium

The buccal epithelium, a non-keratinized stratified layer, exhibits multiple layers with distinct maturation patterns.[22] Cells in the basal layer are competent in dividing and maintaining epithelial population homeostasis. Homeostasis involves segregation, superficial cell proliferation, and desquamation. The intermediate layer contains prickle cells accumulating low molecular weight lipids and cytokeratins. Intracellular lipids are packed into lamellar granules or membrane-coating granules, which move to the cell's apical side, releasing lipid compounds into the extracellular space. The buccal epithelium, characterized by less tight junctions, possesses gap junctions, hemidesmosomes, and glydesmosomes as weak intercellular connections.[23] Resting upon the basal membrane, it forms a continuous interface of irregular saliva between the epithelium and connective tissues. This basal membrane strengthens the barrier property, impeding the flow of large molecules into the buccal mucosa. While oral absorption is not the primary target of FDTs, active ingredient delivery in the buccal cavity alongside the buccal mucosa may facilitate oral absorption. The transfer of drugs via the buccal mucosa involves two pathways: the transcellular pathway, allowing the passage of a lipid and a polar region via cell membranes, and the paracellular pathway, enabling passive diffusion via the extracellular lipid region. The extracellular space lipid matrix plays a pivotal role in the paracellular route's barrier function, particularly for hydrophilic compounds with high molecular weight, such as peptides.[24,25]

1.6. Oral mucosa vascularization

The oral mucosa's vascular network includes lymphatic, arterial, and venous capillaries traversing the multi-layered epithelium and penetrating connective tissues. Originating primarily from the externally present carotid artery, the buccal mucosa receives highly vascularized areas, including the mouth surface, tongue root, and cheek mucosa. Vascular discharge occurs through facial, lingual, and retro-mandibular veins flowing into the inner jugular vein, initiating the first-pass metabolism.[26]

1.7. Salivary flow

Saliva, a crucial factor in disintegrating or dissolving drug formulations, is predominantly injected into the buccal cavity by the sublingual gland, submandibular gland, parotid gland, and various tiny glands. Comprising about 99.5% water, saliva includes electrolytes, gases, phosphorus compounds, mucins, amino proteins, acids, digestive enzymes, proteolytic enzymes, immunoglobulin, and serum albumin. With a weak buffer capacity and a pH range of 6-7, saliva's flow varies between 5.3 and 7.8 during stimulation. The natural salivary flow ranges from approximately 0.1 to 0.2 ml/min, increasing to 6.5 ml/min during stimulation. Saliva hydrates the buccal cavity, and its underlying mucus layer, with thickness varying from 1 to 400 μm, acts as a protective barrier to drug transport.[27]

1.8. The ideal features of FDT

Rapid Dissolution or Disintegration: FDTs exhibit the ability to dissolve or disintegrate within a few seconds when placed in the mouth, obviating the need for water.[28]

High Drug Load Capacity: These tablets allow for a high drug load, facilitating the delivery of an effective therapeutic dose.[29]

Masking of Bitter Taste: FDTs effectively mask the bitter taste of drugs, enhancing patient acceptability and compliance.

Positive Mouth Feel: The formulation of FDTs ensures a pleasant mouth feel during administration, contributing to an improved overall patient experience.

Ease of Transport: FDTs are easy to transport without concerns about fragility, providing a convenient and user-friendly dosage form.

Reduced Sensitivity to Humidity and Temperature: These tablets exhibit lower sensitivity to environmental factors such as humidity and temperature, ensuring stability and efficacy of the drug.

Compatibility with Standard Manufacturing and Packaging: FDTs can be manufactured using standard machinery and packaging processes, contributing to cost-effectiveness in production.

1.9. Requirements of FDTs for an ideal preparation[30]

- It dissolves or disintegrates in a very few seconds in the mouth without the need of water.
- Have low molecular weight.
- To permeate oral cavity tissue for rapid action.
- Ability to partition and diffuse into the epithelial membrane of the upper gastro intestinal tract (log P>1or2).
- It is having a property of taste masking.
- The tablet is not to loose and not too hard.
- It gives pleasant mouth feel.
- It does not leave any residue after oral administration.
- It is not very sensitive to environmental factors (humidity & temperature).
- Using standard manufacturing & packaging equipment to produce tablets at a low cost.

1.10. Advantages of FDT[31]

Administration for Patients Unable to Swallow: Fast Dissolving Tablets (FDTs) offer a viable solution for patients facing difficulty swallowing, including stroke victims, geriatric individuals, those with renal failure, and individuals hesitant to swallow, such as psychiatric, geriatric, and pediatric patients.

Convenient Treatment for Bedridden and Mobile Patients: FDTs prove beneficial for the treatment of bedridden patients with disabilities, as well as individuals with busy lifestyles or those who are frequently traveling and may not have easy access to sufficient water.

Enhanced Mouth Feel and Taste Masking: The superior mouth-feel properties of fast dissolving tablets contribute to a positive shift in the perception of drugs. This is particularly significant in children, as FDTs can improve the taste of bitter medications.

Ease of Administration and Precise Dosing: FDTs offer ease of administration and effective dosing when compared to liquid dosage forms. This characteristic is particularly advantageous for individuals who may struggle with liquid formulations.

Solid Dosage Form Advantages Over Liquid Medicaments: FDTs provide the benefits of solid dosage forms over liquid pharmaceuticals, offering convenience, stability, and ease of handling.

Rapid Drug Absorption from Pregastric Portion: The fast absorption of drugs from the pregastric portion, encompassing the esophagus, pharynx, and mouth, results in a swift onset of action. This feature is crucial for achieving a rapid therapeutic effect.

Minimization of Side Effects through Pregastric Absorption: Pregastric absorption not only facilitates fast drug absorption but also minimizes potential side effects. This, in turn, can lead to improved bioavailability, allowing for reduced dosage while enhancing overall clinical efficiency.

1.11. Disadvantages/limitations of FDTs[32]

Despite their advantages, Fast Dissolving Tablets (FDTs) come with certain limitations:

Mechanical Strength: The primary drawback of FDTs lies in their mechanical strength. These tablets may lack the robustness needed for certain formulations, making them prone to breakage or fragmentation.

Hygroscopic Nature: Some FDTs exhibit hygroscopic properties, making them susceptible to moisture-induced degradation. This requires specialized packaging to maintain physical integrity under normal conditions.

Brittleness: FDTs can be extremely brittle, especially when molded and compressed at low force. This brittleness necessitates advanced peel-off blister packaging, posing challenges in production.

Challenges with Bitter Drugs or Unpleasant Odors: Describing FDTs containing bitter drugs or those with unpleasant odors can be challenging. Special precautions must be taken during the formulation of such drugs to enhance patient acceptability.

1.12. Challenges in developing FDTs[33]

- One of the key challenges in FDT development is ensuring rapid disintegration without compromising the mechanical strength of the tablet.
- Balancing the goal of rapid disintegration with the need to avoid excessive tablet size expansion presents a significant challenge in FDT formulation.
- Striking a balance between achieving rapid disintegration and maintaining adequate tensile strength is crucial for the success of FDTs.
- A challenge is to design FDTs that leave minimal to no residue in the mouth after administration, ensuring a pleasant patient experience.

- Addressing the hygroscopic nature of some FDTs requires effective moisture protection strategies to maintain stability and prevent degradation.
- Developing packaging that is both protective and conducive to easy administration poses a challenge in FDT formulation.
- Ensuring that FDTs are acceptable to patients involves incorporating effective taste masking properties, especially for formulations containing bitter drugs.

1.13. Salient characteristics of FDDDS (Fast Dissolving Dosage Forms)[34]

- Easy administration for psychiatric, geriatric, and pediatric patients who prefer not to swallow medicine.
- Accurate dosing, more convenient than liquid dosage forms.
- No need for water, making it convenient for depressed or epileptic patients.
- Good mouth taste properties, particularly beneficial for children.
- Solid unit dosage forms providing accurate dosing, good stability, small packing size, easy manufacturing, and portability.
- Fast drug dissolution and absorption, leading to rapid action.
- Rapid absorption of drugs from the pregastric portion (oesophagus, pharynx, and mouth), minimizing side effects and improving bioavailability, reducing dose, and enhancing clinical efficiency.

1.14. Techniques for preparing FDTs[35]

- Freeze-Drying or Lyophilization: Involves sublimating the water content of the drug after freezing. Despite its advantages, this technique has drawbacks such as fragility, time-consuming processes, high costs, and challenges with traditional packaging.
- Tablet Moulding: Utilizes solvent and heating methods, with challenges including taste masking and complexities in the process.
- Spray Drying Technique: Involves preparing a porous powder through a spray-drying process, addressing issues related to disintegration and dissolution.

1.15. Sublimation[36]

This process includes incorporating some inert volatile ingredients such as urethane, urea, naphthalene, camphor, etc. and other excipients which was compressed into the tablet. Then this tablet was vacuumed for 30 minutes. At 80 °C for sublimation which creates pores in the tablet structure by the removal of the volatile substance as shown in Fig. 1. This porous tablet dissolves when it reaches to saliva.[9,10] The utilization of non-invasive drug delivery systems is on the rise due to several factors,

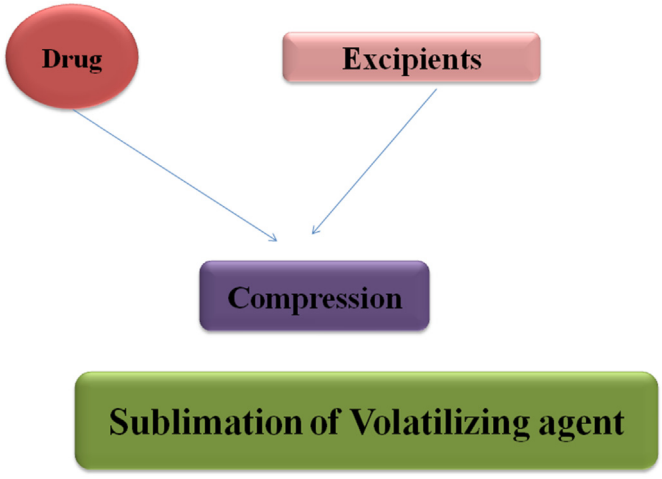

Fig. 1. Process Diagram of sublimation technique for preparation of FDT

including poor patient compliance and acceptance of current delivery methods, limited market space for drug makers, and the escalating costs associated with disease management. The current needs of the pharmaceutical industry revolve around addressing various challenges, including enhancing the half-life, solubility/stability, and bioavailability of poorly soluble drugs. Key issues faced by the biopharmaceutical industry include improving safety by reducing gastrointestinal adverse effects, enhancing organ targeting effectiveness, and improving patient compliance through sustained-release dosage forms or formulations that are easy to swallow. Innovation and the development of new technologies in drug delivery systems are deemed crucial for the survival and competitiveness of pharmaceutical companies. Marketing also plays a pivotal role in the growth of Fast Dissolving Tablets (FDTs). As a medicinal entity nears the end of its patient's life, pharmaceutical companies are compelled to manufacture an updated and improved product, expanding market exclusivity and providing a more suitable drug or dosage form to the patient group. Fast Dissolving Tablets, similar to sustained-release (SR) dosage forms, contribute to an expansion of market exclusivity, leading to increased sales. Despite the higher manufacturing costs associated with advanced dosage forms, this additional cost is not passed on to the users but is considered an investment in meeting patient needs.

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- Fast drug dissolution and absorption, leading to rapid action.
- Rapid absorption of drugs from the pregastric portion (oesophagus, pharynx, and mouth), minimizing side effects and improving bioavailability, reducing dose, and enhancing clinical efficiency.

1.17. Fast dissolving film technique[38]

It consists of a non–aqueous sol. with water–soluble polymers that form films (pullulan, CMC, HPMC, hydroxyethylcellulose, hydroxypropyl cellulose, sodium alginate, polyvinyl alcohol, polyvinyl pyrrolidone), an API and flavouring agent used to create a film when the solvent evaporates. In the case of coated drug micro-particles, bitter drugs, or resin adsorbent can be taken for film formation. The main feature of this method is that these are skinny films that have 2 × 2-inch dimensions which dissolve quickly within 5 seconds, without leaving any residue and feels the good taste.

1.18. Melt granulation[39]

It is a unique method that used superpolystate for preparing fast-dissolving tablets. The term Superpolystates are hydrophilic waxy binders consisting of an M.P 33–370C and the value of hydrophilic and lipophilic balance is 9. Superpolystates act as a disintegrant and as well as binder that builds the physical strength of the tablets, which helps the tablet melting process in the oral cavity and quickly solubilizes without leaving residue. Superpolystates were added by the melt-granulation technique for the preparation of FDTs. Here, granules formation is done from the melted form of this material. For example, paracetamol in crystallized form was used as a drug with CCS and mannitol.

1.19. Effervescent method[40]

Fast dissolving tablets are also prepared by using an effervescent

method. It consists of mixing 12 percent (w/w) concentration of tartaric acid & sodium bicarbonate with super disintegrants like SSG, pregelatinized starch, CCS, and crospovidone. First, tartaric acid and sodium bicarbonate are preheated at 80 °C to evaporate the residual/absorbed moisture and are mixed well into the mortar. Finally, this blend is prepared for compression for the formation of tablets.

1.20. Superdisintegrants

A disintegrating agent allows the tablet to divide into smaller parts when in contact with an aqueous solution. Rapid disintegration of the tablet matrix in the mouth stimulates the swallowing process and enhances the particle size of the tablet, which improves the absorption rate of the API in order to achieve the required therapeutic action.[41] All marketing tablets contain a certain amount of dissolving agent and it is important to know how much and which disintegrating agent is required for the manufacture of a given tablet.[42] The disintegration process begins when a few amounts of saliva or water comes into contact with the tablet and enters the tablet matrix through capillary movement. Hence, for successful development of the formulation, the material properties used as pharmaceutical excipients, matrix structure as well as distribution and pore size should be considered. Since most of the disintegrating agents swell to some degree so swelling pressure is commonly considered to be the major factor of disintegrating tablets. Superdisintegrating or disintegrating agents can be used in the formation of FDTs with sufficient disintegrating qualities at a relatively low extent. They are usually added at a 1-10 percent (w/w percent) level.[43–45] The efficiency of disintegration is related to the concept of force–equivalent technique (combination measurement of the developed water absorption rate and swelling force). The determination of tablet disintegration is usually achieved by critical disintegration conc. mean. Below the critical concentration, the time of disintegration of the tablets is conversely proportional to the conc. of disintegrants and above this conc., the time of disintegration remains constant approximately or uniformly increased. The most important properties of the disintegrating agent are faster swelling without simultaneous viscosity enhancement (without gel formation) due to the high viscosity present on the tablet surface will gradually impede penetration of water into the matrix to disintegrate the tablet. There are many disintegranting and superdisintegranting agent in the market and the majority of these can be used in FDTs. Common examples include croscarmellose, crospovidone, and SSG, and hydroxypropyl cellulose.[46] Crospovidone is a synthetically formed water-insoluble cross-linking homo-polymer with the N-vinyl-2-pyrrolidone chemical structure. For the synthesis of crospovidone polymers, a unique one–step polymerization method termed as “popcorn" polymerization is used. Crosslinking chemically entangles the polymer strings and is a key determinant property of the product. This method produces pores in a structure with tightly cross–linked polymers and a morphology that quickly wipes fluid into the molecule to improve swelling and disintegration. Crospovidone is a non-ionic polymer, so its disintegration characteristics are independent of GIT pH changes.[47] Disintegrating agents are generally water-insoluble substances that swell in the presence of moisture content, so the presence of excess disintegrant can cause nervousness after the disintegration of the tablet.[48] The suitable disintegrating agents and the accurate quantity disintegrant for the formulation of the FDT must be carefully examined. The distribution of the particle size of Polyplasdone XL and Kollidon CL is very similar.[49] However, both the tap and bulk densities differ significantly due to the pores present on the surface of Polyplasdone XL or the smooth surface of the Kollidon CL. Kollidons CL-SF and CL-F possess lower bulk densities than Polyplasdone XL due to their lesser size of particles. The selection of the correct disintegrating agent depends upon the type and method of the formulation. Crospovidone works efficiently as disintegrant by fast swelling property. When crospovidone and mannitol were prepared by using a direct compression technique, the results of the quantity of both crospovidone and mannitol and also the force required for compressing a tablet were studied.[50]

1.21. Direct compression technique

Direct compression is a straightforward method for producing tablets, utilizing traditional equipment, readily available excipients, and minimal processing steps. The addition of disintegrants to Fast Dissolving Tablets (FDTs) facilitates fast formulation disintegration, thus improving the dissolution process. In several FDT technologies based on direct compression, a disintegrating agent influences primarily the disintegration speed and, consequently, dissolution. Super disintegrating agents, such as SSG, calcium silicate, alginic acid, crospovidone, and croscarmellose, are sometimes incorporated in specific amounts to enhance the oral disintegration rate, providing a pleasant sensation. These super disintegrants achieve rapid disintegration by swelling due to water absorption.[51]

1.22. Mass-extrusion technique

The mass-extrusion technique involves softening the composite material using water-soluble components like PEG and methanol as a solvent. The softened material is then extruded through a syringe or extruder to obtain cylindrical-shaped products, which are subsequently cut into tablets using heated blades. The resulting dried cylinders are suitable for coating with granules to mask the bitter taste of drugs.[52]

1.23. Nanonization

Nanonization is a process where the mixture of drug particles is reduced to nanoparticles through a wet milling process. This method is particularly beneficial for low water-soluble active ingredients, enhancing drug bioavailability by reducing the disintegration rate. The process involves compressing these nanoparticles into tablets.[53]

1.24. Cotton candy technique

The cotton candy technique involves forming a polysaccharide matrix by simultaneous quick melting and spinning. This matrix of candy floss is recrystallized, combined with the active drug and excipients, and then compressed using a compression machine to produce FDTs.

1.25. Phase-transition technique

In the phase-transition technique, FDTs are prepared by mixing and compressing a combination of two sugar alcohols—one with a high melting point (M.P) and another with a low M.P. The mixture is heated successively between their melting points, amplifying the bond due to the phase-transition of the lower M.P sugar alcohol, resulting in a hard tablet. This technique is resistant to the rigors of production and transport conditions but may not be suitable for thermally unstable drugs.[54]

1.26. Fast dissolving film technique

This technique involves a non-aqueous solution with water-soluble polymers to form films (e.g., pullulan, CMC, HPMC, hydroxyethylcellulose, hydroxypropyl cellulose, sodium alginate, polyvinyl alcohol, polyvinyl pyrrolidone), an Active Pharmaceutical Ingredient (API), and a flavoring agent. The resulting films dissolve quickly within 5 seconds without leaving any residue, providing a good taste.[55]

1.27. Melt granulation

Melt granulation is a unique method utilizing superpolystate for preparing fast-dissolving tablets. These superpolystates improve tablet physical strength, aiding the melting process in the oral cavity for quick solubilization without residue. For example, paracetamol in crystallized form is used as a drug with CCS and mannitol.[56]

1.28. Effervescent method

Fast dissolving tablets are prepared using the effervescent method by mixing a 12 percent (w/w) concentration of tartaric acid and sodium bicarbonate with super disintegrants like SSG, pregelatinized starch, CCS, and crospovidone. The blend is preheated and then compressed to form tablets.[57]

1.29. Superdisintegrants

Disintegrating agents play a crucial role in allowing tablets to divide into smaller parts when in contact with an aqueous solution. Rapid disintegration stimulates the swallowing process, improving the absorption rate of the Active Pharmaceutical Ingredient (API). Superdisintegrating agents are used in the formation of FDTs for their excellent disintegrating qualities at a relatively low concentration. Examples include croscarmellose, crospovidone, SSG, and hydroxypropyl cellulose.[58]

The efficiency of disintegration is related to the force-equivalent technique, which combines measurements of water absorption rate and swelling force. Disintegrating agents are generally water-insoluble substances that swell in the presence of moisture, and their excess can lead to tablet nervousness after disintegration. Selecting the correct disintegrating agent and determining the accurate quantity for FDT formulation are critical considerations.[59]

Crospovidone is an example of a superdisintegrant that works efficiently due to its fast swelling property. Optimal formulations, such as those containing 13% crospovidone and 34% mannitol, have been suggested to provide specific wetting times and crushing strengths. Various studies have explored the use of disintegrants like L-HPC and MCC in FDT formulations, emphasizing the importance of the type and method of formulation. The selection of the correct disintegrating agent (Table 1) depends on various factors, including particle size distribution, pore size, and material properties used as pharmaceutical excipients.[60]

Table 1
Commonly used Superdisintegrants in FDTs.[61]

Superdisintegrant	Mechanism	Particle size	Nature
Crospovidone	Both wicking and swelling	Particle size- 100 μm	Crosslinked homopolymer of Nvinyl- 2-pyrrolidone
SSG	Uptake of water followed by fast and massive swelling	Insoluble in water. Particle size 140 mesh	Cross–linked low substituted Carboxymethyl–ether of polyglucopyranose
CCS	Swelling	Insoluble in water. Particle size- 200 mesh	Cross–linked form of CMC
Derivatives of acrylic acid	Wicking action	Dispersed in cold water, insoluble in organic solvents	Poly(acrylic acid) highly porous hydrogel
Sodium alginate	Swelling	Slowly solubilized in water, hygroscopic characteristics	Sodium salt of the alginic acid
NS-300	Wicking type	Particle size –106 μm	Carboxy methyl cellulose (CMC)
Effervescent mixture	Effervescence	Crystalline nature	Sodium bicarbonate, citric acid, sodium salt of alginic acid, tartaric acid
L-HPC	Both wicking and swelling	Particle size–106 μm	Low hydroxylpropyl cellulose
ECG-505	Swelling type	Particle size–106 μm	Calcium salt of CMC

1.30. Mechanism of disintegration[62]

The process of converting large tablet particles into fine particles involves various mechanisms.

1.31. Through capillary action

Capillary action initiates tablet disintegration by allowing the medium to enter the tablet when placed in an aqueous medium or water. This entry removes air from the molecules, weakening intra-molecular bonds, and facilitating the disintegration of large tablet particles into smaller ones.

1.32. Through swelling mechanism[63]

Swelling is a commonly accepted method for tablet disintegration. High-porous tablets may disintegrate poorly due to insufficient swelling force. The compression force should be optimized to prevent reduced disintegration rates.

1.33. Through air expansion mechanism[64]

Disintegrating agents with exothermic properties, such as CCS and SSG, become wetted and release localized stress due to the expansion of air present in the capillaries. This expansion increases tablet disintegration.

1.34. Through disintegrating particle/particle repulsion theory[65]

This mechanism involves tablet swelling using a ‘non-swellable' disintegrating agent. The particle repulsion theory, proposed by Guyot-Hermann, explains tablet swelling with non-swellable particles causing tablet disintegration.

1.35. Through deformation process[66]

During tablet compression, dissolved molecules deform. Upon contact with the aqueous medium, these deformed molecules regain their normal structure, leading to disintegration. Enhanced swelling properties of starch occur when granules are largely deformed during compression.

1.36. Through release of gases[67]

Moist tablets release carbon dioxide when tartaric acid or citric acid interacts with bicarbonate and carbonate. The tablet disintegration results from the pressure produced inside the tablet due to gas production. Environmental conditions during tablet manufacturing must be precisely controlled.

1.37. Through enzymatic reaction[68]

Enzymes in the systemic circulation act as disintegrating agents. These enzymes break the binding properties of the binder, aiding in tablet disintegration.

1.38. Taste masking approaches[69]

Effective taste is crucial for patient acceptance, and various approaches are employed for taste masking. This is a simple and effective method, particularly for liquid formulations, chewable tablets, and pediatric formulations. Artificial flavors and sweeteners, such as aspartame, are commonly used to reduce the bitterness of drugs.

1.39. Lipids[70]

Lipids, oils, polyalcohol, and surfactants increase mouth viscosity,

acting as taste-masking agents by coating taste buds. For example, guaifenesin exhibits better taste when blended with magnesium aluminum silicate and carnauba wax, then melt-granulated.

1.40. Lecithin and lecithin-like substances[71]

Pharmaceutical products with an excess of lecithin/lecithin-like ingredients are used to control bitter taste. These substances are mixed with other excipients to form a granulated, masked taste composition.

1.41. Coating of hydrophilic vehicles[72]

Coating serves as a protective barrier, minimizing contact between the drug and sensory receptors. Micro-emulsion technology is used for masking the taste of bitter powders, chewable tablets, and liquid suspensions.

1.42. Carbohydrates (cellulose)

Carbohydrate coatings are employed to mask the bitter taste of oral medicines. Coating polymers with cellulose or shellac mixtures and a second film-forming polymer soluble at pH $>$ 5 can mask the bitter taste of drugs.

1.43. Inclusion complexation

This method involves forming stable inclusion complexes between drug particles and complexing agents. Cyclodextrin is commonly used to suppress the bitter taste of formulations with low doses.

1.44. Solid dispersion method

Solid dispersion involves dispersing active ingredients into an inert carrier or solid-state matrix, providing an effective method for taste masking. This method is beneficial for the masking of bitter medicines with low water solubility.

1.45. Prodrugs

Prodrugs are chemical-modified inert parent compounds that release the pharmacologically active parent drug upon biotransformation. Prodrugs with tasteless properties are formulated to improve buccal delivery without the characteristic bitter taste.

1.46. Ion exchange resin

Ion-exchange resins are used for taste masking, possessing high molecular weight and insoluble poly electrolytes that exchange mobile ions with the surrounding medium. This stoichiometric and reversible exchange helps mask the taste.

2. Conclusion

In conclusion, the development and acceptance of Fast Dissolving Tablets (FDTs) mark a significant advancement in oral drug delivery systems. These tablets offer a promising solution to the challenges associated with traditional dosage forms, especially for individuals with difficulties in swallowing, such as pediatric and geriatric patients. The unique properties of FDTs, including rapid dissolution or disintegration without the need for water, high drug load capacity, and effective taste masking, make them a convenient and patient-friendly alternative.

The anatomical and physiological characteristics of the buccal cavity play a crucial role in the absorption of drugs through the buccal mucosa, contributing to the rapid onset of action associated with FDTs. Understanding the complexities of the buccal epithelium, oral mucosa vascularization, and salivary flow provides a foundation for optimizing drug formulations and enhancing therapeutic outcomes.

While FDTs offer numerous advantages, including ease of administration, precise dosing, and rapid drug absorption, they are not without limitations. Challenges such as mechanical strength, hygroscopic nature, and taste masking for bitter drugs need to be addressed in the formulation and development process. Overcoming these challenges is essential to maximize the potential benefits of FDTs in improving patient compliance and overall therapeutic efficacy.

The pharmaceutical industry's increasing focus on non-invasive drug delivery systems, coupled with the demand for enhanced bioavailability and patient acceptance, underscores the importance of innovative formulations like FDTs.

CRediT authorship contribution statement

Shubhrat Maheshwari: Conceptualization. **Aditya Singh:** Methodology. **Aditya Prakash Varshney:** Conceptualization, Methodology. **Anurag Sharma:** Writing – original draft, Writing – review & editing.

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