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A Comprehensive Review on Progress and Challenges in Technology of Orodispersible Tablets

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ABSTRACT: Numerous medications that absorb through the buccal cavity have been explored in connection to orodispersible tablet dosage forms because of their many benefits, which include stability, fast onset of action, water-free administration, precise dosing, ease of production, better bioavailability, compact packaging, and easy handling (1–5). Conventional Oro dispersible tablets have been linked to drawbacks such a lack of mechanical strength, an inclination for sugar, and the absence of an option for regulated or delayed release, if not cooked properly, an unpleasant flavor and grittiness on the tongue (5–8). Oro dispersible tablets are solid dose forms that dissolve quickly in saliva and are not likely to cause drowsiness or a delayed start to action.(8–10) They have been researched to increase bioavailability with the goal of either increased compliance effects or a quick onset of action.(11–14) In order to obtain successful outcomes, precise and intricate manufacturing and characterization processes must be taken into account throughout the design and development of innovative Orodispersible drug delivery systems.

Keywords: Oro dispersible tablet; buccal absorption; accurate dosing; mechanical strength; bioavailability enhancement; fast onset of action; improved compliance.

I. INTRODUCTION

Orodispersible medication administration is a crucial strategy for treating both systemic and local illnesses. (15) The oral route offers several benefits, including improved compliance from patients and safety, ease of use, simplicity, and affordability. (6–8,16–22) The unique properties of the buccal/oral pathway offer substantial potential for the use of numerous bioactive substances. However, when designing an Oro dispersible tablet formulation, several issues must be taken into consideration. Among these concerns are flavor making, mechanical strength, hygroscopic nature, medication load, cost of production, special packaging needs, and patient compliance. (5,23)

Orodispersible methods for delivering drugs have traditionally been employed to provide pediatric/geriatric friendly tablets and these intended to provide medical care for individuals with dysphagia problem. Although systemic distribution of other pharmaceuticals has additionally been investigated, the buccal route has historically been employed mostly for the ingestion of locally active medications such as analgesics, antihistamines, antipsychotics, antiemetics, and caffeine. (8,9) In the previous few years, Orodispersible tablet formulations have become the subject of much research thanks to SeDeM experts. The compressibility and buccal dispersibility of components are evaluated by the SeDeM expert system to determine their eligibility for Oro dispersible tablet compositions. (24) Beyond conventional Oro dispersible tablet formulations and medications, research is currently being conducted on co-processed excipients, innovative production processes including 3D printing and hot melt extrusion, and studies indicate that these novel approaches merit more study. (24–27)

II. ANATOMY OF ORAL MUCOSA

The oral mucosa is composed of a thicker lamina propria & stratified squamous epithelium. The stratum basal (base layer), stratum spinosum (prickle layer), stratum granulosum (granular layer), and stratum corneum (outermost layer) are the four layers of the epithelium in keratinized oral mucosa. The outside strata of nonkeratinized epithelium are additionally referred as the superficial and intermediate layers, but stratum spinosum and basal layers stay the same. The oral epithelium can be nonkeratinized or keratinized, depending on the region. Whereas keratinized epithelium is present on the gingiva, hard palate, and the dorsal surface of the tongue, nonkeratinized squamous epithelium lines the soft palate, inner lips, cheeks, floor of the mouth, and ventral tongue surface. Stratified squamous epithelium and a thicker lamina propria comprise the oral mucosa. The stratum basal (base layer), stratum spinosum (prickle layer), stratum

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granulosum (granular layer),and stratum corneum (outermost layer) are the four layers of the epithelium of the keratinized oral mucosa. The stratum spinosum and bottom layers of nonkeratinized epithelium remainunchanged, however the surrounding layers are recognized as the superficial and intermediary strata. Based on the area, possibly, the oralepithelium keratinized or nonkeratinized.Nonkeratinized squamous epithelium borders inner lips,delicate palate,cheeks,the tongue's ventral surface and the interior of the oral cavity, while keratinized epithelium encompasses the gingiva, The tongue's dorsal portion and the hard palate. When In the stratum granulosum, keratinocytes divided into nonvital surface cells or squamous cells then stratum corneum gets formed. Cells go through terminal differentiation when they go towards the base of the stratum, which contains progenitor cells, to the external strata. Nonkeratinized epithelium is devoid of keratinized surface layers, unlike keratinized epithelium. However, in contrast, friction or chemical stress can cause nonkeratinized tissue to change into keratinizing epithelium, which results in hyperkeratinization. Hyper keratinization is indicated, for instance, via the formation of the Linea alba, a white, calloused tissue ridge along the buccal mucosa where the mandibular and maxillary teeth converge. This tissue has a keratin-rich surface and displays every stratum of orthokeratinized tissue, including keratin's layers and granules. The hyperkeratinized region in the oral mucosa of patients who grind their teeth extends past the Linea alba, generating a bigger, rougher, white lesion that ought to be mentioned in the patient's dental care plan for the purpose of addressing their parafunctional habits. (4,28,29)

III. FORMULATION AND PREPARATION OF ORODISPERSIBLETABLETS:

Direct Compression:

The simplest way to make tablets is via direct compression. It requires fewer processing stages, commonly available excipients, and conventional equipment. High medication dosages can also be accommodated through this method, enabling the final tablet weight to be greater than that of other production methods. (30)

Tablet moulding: -

Using less pressure than with standard tablet compression, a hydro-alcoholic solvent is mixed with water-soluble components and shaped into tablets. After that, the solvent evaporates by air drying. Because moulded tablets are less compact and have a porous structure, they dissolve and disintegrate morequickly, improving absorption in the process (31).

Spray Drying: -

employing sodium starch glycolate or croscarmellose sodium as disintegrating agents, mannitol as a bulking agent, hydrolyzed and non-hydrolyzed gelatins as bolstering substances&an acidic (like citric acid) or alkaline (like sodium bicarbonate) substance to encourage disintegration and dissolution. (31)

Disintegration Addition Method:

To promote quick dissolution and disintegration this procedure involves adding super disintegrantsin formulation at the ideal concentrations. Examples include low-substituted HPEC, sodium starch glycolate, crystalline cellulose (Avicel PH-102), crospovidone, and sodium croscarmellose. (32,33)

Lyophilization: -

An aqueous carrier solution is accustomed to dissolve or distribute the medication before being included into the wells of blister packs that have already been produced. To harden the medication solution, these trays are put through a freezing tunnel filled with liquid nitrogen. The blister packs are frozen and after which put in the refrigerator cabinets to continue the freeze-drying process. The blisters are packaged and mailed after the procedure is finished. Due of its broad surface area and high porosity, the finished product dissolves quickly and has improved absorption and bioavailability. (34)

Mass Extrusion:

By using a methanol and water-soluble polyethylene glycol solvent combination, this approach softens the active mixture. After the material has softened, it is pushed or extruded through a syringe to form a cylindrical shape. To produce tablets, this shape is divided into even sections using a hot blade. (7)

Sublimation:

Compacted into tablets, inert solid substances that evaporate fast, such as ammonium bicarbonate, urea, camphor, and ammonium carbonate, and hexamethylene tetramine, were combined beside the other tablet constituents.

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Sublimation was then used to eliminate the volatile materials, resulting in a porous structure. (12)

IV. PATENTED TECHNOLOGIES:

Flashtab technology:

The active component of tablets made with this method is present in the form of microcrystals. Conventional techniques including coacervation, microencapsulation, and extrusion-spheronization could be used to create drug microgranules.Throughout,conventional tablet production methods are used. (35)

Wow tab technology:

WOW represents "Without Water." To create a powerful, quickly dissolving tablet, a blend of saccharides with low and high moldability is utilized in this procedure. Before the active component is compacted into ablet, it is combined with a low-moldability saccharide, such lactose, glucose, mannitol and then granulated using a high-moldability saccharide, like maltose or oligosaccharides. (21)

Ziplet technology: -

Given that it may be paired with Eurand's cutting-edge particle technologies, including the market-leading Microcaps® taste-masking system and Diffucaps® controlled release technology, AdvaTab distinguishes itself from different orally disintegrating tablet solutions. Improved taste and a smooth mouthfeel are combined with AdvaTab to create a dose form that is more patient-friendly. (10)

V. TECHNOLOGICAL CHARACTERIZATION

Technological Numerous esthetics, chemical (such as pH, drug content, release), physical (such as weight, size, thickness, morphology), mechanical (hardness, friability, etc.), and performance characteristics accustomed to characterize orodispersible tablets. Although general assessment techniques have been employed, to thoroughly examine this dose form, modifications or novel techniques usually require to be created. The most significant tests that have been brought to the attention to characterize orodispersible tablets are compiled inside Table 1.

Table 1. Technological characterization of Orodispersible Tablets: -

Evaluation Parameter	Principle	Methodology	Reference
Hardness	determines how resistant the tablet will be compressed while under pressure.	Using a hardness tester, determine how much force is needed to shatter the tablet.	1,6,8,11,21,24
Friability	evaluates the tablet's resistance to breaking and abrasion during handling.	Once the pills have been rotated in a friabilator, calculate The proportion of weight lost.	1,6,8,15,21,24
Wetting time	determines how long the tablet must remain moist on a water surface.	Observe how long It requires the tablet to completely get saturated after placing it on damp tissue paper.	1,6,8,10,15,21,24,
Disintegration	determines how long it will take a pill to dissolve into smaller pieces in a given medium.	Measure how long it takes the pill to disintegrate completely in a specified medium.	1,6,8,9,10,11,15,17,21,24
Dissolution	determines how quickly and how much of the active component is released into solution from the tablet.	Using a dissolving instrument, determine the tablet's medication release volume and pace.	1,6,9,15, 17,24,
Thickness	guarantees that the tablet's dimensions are consistent.	With a vernier caliper, find the tablet's thickness.	3,6,8,11,21,
Water Content	calculates how much water is into the tablet.	Karl Fischer titration can be applied to find the water	3,10,15, 24,

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		content.	
Moisture content	establishes the amount of moisture, the tablet takes in from its surroundings.	A moisture analyzer may be employed to ascertain the amount of moisture.	4,
pH	determines the tablet's solution's acidity or alkalinity.	Using a pH meter, find the pill dispersion's pH in water.	4,
Evaluation Parameter	**Principle**	**Methodology**	**Reference**
Physical appearance	evaluates the tablet's color, form, and general aesthetic qualities.	Examine the tablets' color, form, and texture with your eyes.	6,21,
Weight variation	makes certain that each tablet inside a batch weighs the same amount.	Weigh each tablet separately and calculate the mean weight to ensure consistency.	6,21,24,
Taste	assesses the tablet's palatability after it dissolves inside the mouth.	Analyze the flavor with your senses or with an electronic tongue.	6,24
Assay	calculates the amount of the tablet's active medicinal component.	Use an appropriate analytical technique, such as HPLC, to quantify the quantity of the active component.	6,21,
Morphology	looks at the tablet's outside and inside design.	Use scanning electron microscopy to examine the internal structure and surface.	9,10,
Surface area	determines the tablet's total surface area, which has an impact on the rate of breakdown.	Applying BET (Brunauer-Emmett-Teller) analysis, find surface area.	10,
Texture	evaluates how the tablet feels inside the mouth or when it's handled.	Using an analyzer of textures, evaluate the texture.	10
Porosity	establishes the tablet's pore volume, which influences how easily it dissolves and disintegrates.	Mercury intrusion porosimetryis applicable to find the porosity.	15,

It is required to design efficient algorithms and key techniques for regulating tablet qualities, including their mechanical, chemical, and physical aspects, additionally for assessing toxicity and bioactivity. The chemical and physical characteristics of tablets feature a significant impact on in vitro drug release and film pharmacokinetics.

To investigate every conceivable combination of every element at every level and for the purpose of maximizing the composition inside the formulation, factorial design and the desire function are employed. This tool helps specify manufacturing phases and optimize time and resources in the early stages of product development. (36)Qualitative assessment is crucial to be capable of determining, identifying, and ultimately choosing one orodispersible tablet formulation. Organoleptic properties are easilyevaluated;however, they cannot be measured objectively. Assessing appearance, color, odor, and transparency are the principal characteristics.

Orodispersible tablets are defined by their physical attributes, which include hardness, thickness, and surface shape. Regarding stability

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over time, controlling the orodispersible tablets' pH and moisture content is crucial. (4) The medication content and content homogeneity both inside and across tablets from the same batch are additional general standards for the evaluation, additionally orodispersible tablet quality control. Regarding the mechanical properties of tablet several authors have used texture analyzers or other equipment's of force measurement to assess tensile strength as a sign of tablet strength. The ultimate tensile strength is the force per unit cross-sectional area required to break the tablet. The following formula is employed in todetermine the tensile strength and record the load at the point of rupture:

$$T = \frac{2F}{\pi d t} \quad \text{---------- (1)}$$

Where F is the crushing load, and d and t signify the diameterand tablet's thickness, respectively. (17,26,27,37)

Tablet's bio adhesive behavior depends on their capacity to hydrate when coming into touch with saliva, which greatly affects stability, drug release patterns. The swelling index is calculated using the Eq. 2:

$$\textbf{Swelling index} = \frac{w_t - w_0}{w_0} \textbf{---------(2)}$$

where the pill's weight at time t is represented by w_t, and weight at time zero by w_0(37).

For the purpose of evaluating the therapeutic and safety of orodispersible tablets, biological effects research must be prioritized above technological characterization. Several of the published toxicological assessment of orodispersible tablets include potential allergens and irritants, (38) long term stability, (39) dissolution &disintegration. (40)

VI. APPLICATIONS

Analgesics:

Significant developments have been done within the domain of analgesic orodispersible tablets (ODTs) In the past several years, especially in formulation technologies and patient-centric applications. ODTs are perfect for patients who have trouble swallowing, including older and pediatric patients, since they break down swiftly within the oral cavity without requiring water.(6) Utilizing co-processed excipients and super disintegrants, which increase mechanical qualities and accelerate the disintegration process, are innovations as part of the planning for preparing ODTs.(41) Additionally, inclusion of nanoparticles into ODT formulations has been a breakthrough, optimizing drug delivery efficiency and expanding The range of medications that are available for use via this route.(6)

Third-generation ODTs with altered release profiles, like tablets with coated micropellets or microcapsules that enable prolonged drug release, are another recent trend. (41) Innovative production techniques, like 3D printing, have made it possible to create customized ODTs that are suited to the demands of specific patients. These developments increase the bioavailability aspect of analgesic medications additionally improves patient compliance, which both increase the medications' effectiveness in the treatment of pain. (42)

Antihistamines:

Significant progress has been made within the domain of antihistamine research recently, particularly in the creation of orodispersible tablets (ODTs). These pills are very useful for individuals that have trouble swallowing regular pills, such Psychiatric, pediatric, and elderly patients. They are made to swiftly melt in tongue without requiring water. One noteworthy instance is the creation of a dual-purpose orodispersible tablet comprising meclizine HCL that combines extended and faster drug release to improve therapeutic effectiveness. (43) Using nanoparticles and super disintegrants, this novel strategy aims to provide both fast release from the buccal cavity and delayed absorption in the gastrointestinal tract1. The effectiveness and Patient compliance to these dose forms have also been enhanced by developments in preparation technologies, like the implementation of 3D printing and the creation of third-generation ODTs with changed release characteristics.(41) Research has also demonstrated the increased safety and effectiveness among the most recent generation of antihistamines, which means these are the first choice for treating ailments including urticaria and allergic rhinitis.(44) These developments underscore The potential for ODTs to revolutionize administering of antihistamines, offering a more patient-friendly and effective treatment option.

Antipsychotic:

Antipsychotic orodispersible tablets have showed great potential Regarding enhancing compliance of patients and treatment results, according to recent research and breakthroughs in the area. The appearance of cariprazine orodispersible tablets, which have shown during

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clinical trials to be bioequivalent to conventional hard gelatin capsules, is one noteworthy breakthrough. (45) Furthermore, to improving the disintegration and dissolving properties of ODTs to ensure an instant onset of action, this new formulation provides an alternative for those suffering from schizophrenia who might have trouble swallowing traditional tablets. Novel excipients and the nanoparticle's integration have further improved the efficiency of drug delivery. (46) Furthermore, generating ODTs with regulated release has broadened their use and enabled long-lasting therapeutic benefits. (47) These developments not only address the issues Regarding medication compliance but also provide a more accessible and effective treatment alternative for people with mental diseases. (8,18,19,48,49)

Table 2: RECENT PATENTS ON ORODISPERSIBLE TABLETS: -

Author/Year	General Technological ODT Characteristics	Polymers/Bio adhesive Substances Included	Others Excipients Included	Claims
Emrah ozakar, rukiye sevinc ozakar, bedran altog/2022	Combination of indomethacin & famotidine by lyophilization, direct compression, sublimation technique	PEG4000, Kollidon CL	Sodium saccharin, Sucralose, Distilled water, Lactose monohydrate, croscarmellose sodium, MCC	ratio of indomethacin to famotidine is 25:20.
Christian F. Wertz Tzehaw Chen Joseph McTarsney Sarah M. Rieschl Limin Shi/2021	Pharmaceutical formulations including amorphous solid dispersions of nilotinib, an inhibitor of protein kinase.	HPMC-AS, methacrylic acid or ethyl acrylate copolymer, Eudragit L100-55	Mannitol, Croscarmellose Sodium, Colloidal Silica, Magnesium stearate, crospovidone,	Nilotinib, the polymer isexisting inside the amorphous solid dispersion in a w/w ratio of 35:65 to 80:20 (nilotinib: polymer)
María Carmen LLUCH LORES Xavier FORMOSA MÁRQUEZ Almudena DOMÍNGUEZ FERNÁNDEZ Diego TORREA GOÑI/2021	orodispersible solid dosage form of rasagiline, encapsulated in a polymer matrix, designed for rapid disintegration and specific dissolution profiles in varying pH condition	HPMC, Polyacrylic resin C100NaMR and C115KMR,	mannitol, peppermint flavor, menthol flavor, acesulfame K, lactose monohydrate, resin IR-120, sodium stearyl fumarate, magnesium stearate	In order to treating idiopathic Parkinson's disease, ODT form comprises a therapeutically effective dosage of rasagiline or a salt that is accepted by the FDA. The salt is enclosed in a matrix that enables unique dissolving profiles at certain pH levels.

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VII. REMARKS AND FUTURE CONCLUSIONS

This thorough analysis has brought to light both the major developments and difficulties in the creation of orodispersible tablets. The conversation summarized ODT's value in enhancing patient adherence, particularly for groups that profit from their quick start of operation and simplicity of administration—children, the elderly, and people who possess dysphagia, for example. Technological advancements, such as new production techniques like sublimation, lyophilization, and 3Dprinting, have been essential in resolving the inherent problems with ODT formulation, suchmoisture sensitivity, mechanical strength. Moreover, thelaunch of cutting-edge excipients and proprietary technology has expanded the therapeutic uses of ODTs beyond analgesics to include antipsychotics, while also improving the speed when the tablet dissolve and disintegrate.

Understanding the specific oral mucosa's anatomical characteristicsis vital about the development and design of successful formulations, since these features have a significant impact on bioavailability and medication absorption of ODTs. Furthermore, the described technical characterization techniques are crucial to guaranteeing the safety, effectiveness, and the standard of ODTs, which makes them dependable substitutes for traditional dosage forms.

Finally, even though ODTs have come a long way, Numerous issues still exist that require attention. These include maintaining drug content consistency, maintaining stability in a range of environmental settings, and improving patient-centered design. These difficulties will demand further investigation and creativity. ODTs appear to have a promising future. ahead of them, with the potential of wider therapeutic uses because to ongoing advancements in manufacturing and formulation research. By combining these developments, more patient-friendly, more efficient drug delivery systems will probably be created, meeting unmet requirements across a range of therapeutic domains.

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