Fast dissolving Buccal film: A comprehensive Review

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Abstract
Fast dissolving buccal films (FDBFs) have emerged as a promising drug delivery system, offering advantages such as ease of administration, improved patient compliance, rapid drug dissolution, and potential for enhanced bioavailability. This abstract provides an overview of the future prospects of FDBFs based on ongoing research and development in the field. Future advancements in FDBFs involve improved formulation techniques, including the exploration of different polymers, excipients, and additives to optimize film integrity, drug release, and mucoadhesive properties. Additionally, the integration of nanotechnology in FDBFs is being investigated, with a focus on nanostructured films and nanocarriers to enhance drug solubility, stability, and permeability. Combination therapies within FDBFs are anticipated, allowing for the simultaneous or sequential delivery of multiple drugs, enabling personalized treatment regimens. Targeted and controlled drug delivery mechanisms, such as the incorporation of targeting ligands or stimuli-responsive systems, are being explored to achieve site-specific drug release. Furthermore, the inclusion of theranostic capabilities in FDBFs, combining therapeutic agents with diagnostic functionalities, holds promise for real-time monitoring of drug release, drug localization, and disease response. Patient-centric design considerations, including taste masking, ease of administration, and aesthetic appeal, are expected to drive future developments in FDBFs, particularly for paediatric and geriatric populations. The integration of FDBFs with digital health technologies, such as smart sensors or electronic monitoring systems, is also anticipated to revolutionize medication management and enable personalized therapy. Overall, the future of fast dissolving buccal films is promising, with ongoing research and development focused on improving formulation techniques, expanding applications, and incorporating novel technologies. These advancements have the potential to enhance drug delivery efficacy, patient compliance, and personalized therapy, ultimately improving patient outcomes.

Key words: FDBFs, Polymers, theranostic capabilities, Patient-centric design, digital health technologies.

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Introduction

Fast dissolving buccal films (FDBFs) have gained significant attention in recent years as an innovative drug delivery system. These thin films, designed to be placed on the buccal mucosa, offer several advantages over traditional dosage forms, including rapid dissolution, improved bioavailability, enhanced patient compliance, and ease of administration [1].

Fast dissolving buccal films typically consist of a polymeric matrix loaded with active pharmaceutical ingredients (APIs). The selection of suitable polymers is crucial to achieve optimal film properties. Some commonly used polymers include hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), sodium alginate, pullulan, polyvinyl alcohol (PVA), and their combinations. These polymers contribute to film strength, flexibility, and disintegration properties [2-3].

Fast dissolving buccal films offer a versatile platform for the delivery of various drug classes, including analgesics, antihypertensives, antiemetics, antidiabetics, antipsychotics, and anti-asthmatics [4]. The buccal route provides direct access to the systemic circulation via the rich vascular network of the oral mucosa, bypassing first-pass metabolism and gastrointestinal degradation. FDBFs have demonstrated efficacy in improving drug

bioavailability, achieving rapid onset of action, and providing controlled release profiles. Moreover, they are particularly useful for paediatric, geriatric, and dysphagic patients who face difficulty swallowing conventional dosage forms [5].

Role of polymers in FDBFs

Polymers play a crucial role in the formulation of fast dissolving buccal films (FDBFs) by providing structural integrity, controlling drug release, enhancing mucoadhesion, and improving patient acceptance. The selection of appropriate polymers is essential to achieve desired film properties and optimize drug delivery [6]. Here are the key roles of polymers in FDBFs:

Matrix Formation: Polymers serve as the main component of the film matrix, providing mechanical strength and flexibility. They form a three-dimensional network that holds the active pharmaceutical ingredient (API) and other excipients together. The choice of polymer determines the film's thickness, disintegration time, and mechanical properties [7].

Rapid Dissolution: FDBFs are designed to dissolve quickly in the buccal cavity, ensuring rapid drug release and absorption. Polymers with good water solubility, such as hydroxypropyl cellulose (HPC) and polyvinyl alcohol (PVA), enable fast dissolution of the film upon contact with saliva. This property is crucial for achieving rapid onset of action and improving bioavailability [8].

Mucoadhesion: Mucoadhesion refers to the ability of a film to adhere to the buccal mucosa, prolonging residence time and enhancing drug absorption. Certain polymers, such as sodium alginate and hydroxyethyl cellulose (HEC), possess mucoadhesive properties. They interact with the mucus layer and epithelial cells, promoting intimate contact and prolonged drug release at the site of application [9].

Drug Release Control: Polymers play a vital role in controlling the release of the drug from the FDBFs. By selecting polymers with different swelling and erosion characteristics, the drug release rate can be tailored to achieve sustained, controlled, or pulsatile release profiles. For example, hydrophilic polymers like HPC and pullulan swell upon hydration, leading to controlled drug release over time [10].

Stability and Protection: Polymers help protect the API from degradation and provide stability to the film formulation. They act as a barrier, preventing exposure to environmental factors such as light, moisture, and oxygen, which can degrade the drug. Polymers like PVA and Eudragit® can provide excellent film protection and stability [11].

Taste-Masking: Some drugs have unpleasant tastes, which can lead to patient non-compliance. Polymers can be utilized to mask the bitter or unpleasant taste of the drug by forming a barrier between the taste buds and the drug molecules, enhancing patient acceptability and compliance [12].

Therefore, the judicious selection and combination of polymers in FDBFs are critical for achieving optimal drug release, mechanical properties, mucoadhesion, and patient acceptability.

Formulation of FDBFs

Polymers: Various polymers are used in the formulation of fast dissolving buccal films (FDBFs), each offering specific advantages in terms of film properties and drug delivery. Here is a list of commonly used polymers categorized based on their classification and their respective applications in FDBFs, shown in table no.1

Table No.1 Type of polymer with suitable examples

S.No.	Category of polymers	Examples
1.	**Cellulosic Polymers**	• Hydroxypropyl cellulose (HPC) • Hydroxyethyl cellulose (HEC) • Ethyl cellulose • Methyl cellulose • Sodium carboxymethyl cellulose (NaCMC) • Hydroxypropyl methylcellulose (HPMC) • Microcrystalline cellulose
2.	**Synthetic Polymers**	• Polyvinyl alcohol (PVA) • Polyvinylpyrrolidone (PVP) • Polyethylene glycol (PEG) • Eudragit® polymers (e.g., Eudragit® E, RS, RL, S, L) • Polyvinyl acetate (PVA) • Methacrylic acid copolymers (e.g., Eudragit® Eudragit® RS, RL, RLPO)
3.	**Natural Polymers**	• Sodium alginate • Chitosan

		• Pullulan • Gelatin • Xanthan gum • Guar gum
4.	**Combination Polymers**	• HPC and HEC combinations • HPMC and PVP combinations • PVA and HPMC combinations

Each polymer possesses distinct characteristics, such as film-forming ability, mechanical strength, swelling behaviour, mucoadhesive properties, drug release control, and stability. The selection and combination of polymers depend on the desired film properties, drug characteristics, and specific application requirements.

It is important to note that the selection of polymers may vary depending on the specific formulation, drug compatibility, and regulatory considerations. Hence, formulation scientists must carefully choose the polymers based on their intended objectives and the desired performance of the FDBFs. [13-18]

Mechanism of action of polymers on release of drug: Polymers used in the formulation of fast dissolving buccal films (FDBFs) play a critical role in controlling the release of drugs. The mechanism of action of polymers on the release of drugs can be attributed to several factors, including polymer swelling, erosion, diffusion, and matrix formation. Here is an overview of the mechanisms by which polymers influence drug release:

Swelling and Hydration: Many polymers used in FDBFs are hydrophilic and have the ability to absorb water and swell. When the film comes into contact with saliva or buccal fluids, these polymers rapidly imbibe water, leading to film swelling. The hydrated polymer matrix creates spaces or channels that allow the drug to diffuse out of the film. Swelling of the polymer matrix can enhance drug dissolution and promote faster drug release [19].

Erosion and Disintegration: Some polymers are designed to undergo erosion or disintegration upon exposure to saliva or buccal fluids. As the polymer degrades or dissolves, it releases the entrapped drug molecules into the surrounding medium. The erosion rate can be controlled by the polymer composition, molecular weight, and cross-linking density. This mechanism is particularly useful for achieving sustained or controlled drug release profiles [20].

Diffusion through the Polymer Matrix: Polymers can act as barriers, impeding drug diffusion and controlling release. Drug molecules dissolve or disperse in the polymer matrix and diffuse through it to reach the surface or interface between the film and the surrounding environment. The rate of drug diffusion is influenced by the polymer properties, including molecular weight, chain mobility, and drug-polymer interactions. Polymers with lower molecular weight and higher diffusivity facilitate faster drug release [21-22].

Matrix Formation: Polymers form a matrix structure within the buccal film, entrapping the drug and influencing its release kinetics. The drug is distributed or dispersed within the polymer matrix, and the release occurs through a combination of diffusion and dissolution. The polymer matrix provides a reservoir for drug release, allowing sustained or controlled release profiles based on the polymer characteristics and drug-polymer interactions [23].

pH and Ionic Effects: Some polymers are sensitive to pH or ionic strength changes, which can affect drug release. For example, polymers like Eudragit® exhibit pH-dependent solubility or swelling behaviour. These polymers can release the drug selectively based on the environmental pH conditions, such as the pH gradient across the buccal mucosa [24-25]

Excipients: In addition to polymers, fast dissolving buccal films (FDBFs) often contain various excipients to improve their performance, stability, and patient acceptability. Excipients are non-active ingredients that assist in the formulation process and enhance the characteristics of the final product. Here are some commonly used excipients in FDBFs [26]:

Plasticizers: Plasticizers improve the flexibility and elasticity of the film, making it less brittle and more comfortable for the patient. Examples of plasticizers used in FDBFs include polyethylene glycol (PEG), propylene glycol (PG), glycerin, and sorbitol [27].

Sweeteners: To enhance palatability and patient compliance, sweeteners are added to mask the bitter taste of drugs or the unpleasant taste of the film itself. Common sweeteners used in FDBFs include sucralose, aspartame, mannitol, and xylitol [28].

Flavouring Agents: Flavouring agents are employed to improve the taste and provide a pleasant sensory experience. They can include natural or artificial flavors such as mint, fruit flavours, or other suitable taste-masking agents [29].

Disintegrants: Disintegrants aid in the rapid disintegration or dissolution of the film upon contact with saliva. They facilitate the quick release of the drug for absorption. Examples of disintegrants used in FDBFs

are crosspovidone, sodium starch glycolate, and croscarmellose sodium [30].

Surfactants: Surfactants can enhance wetting and improve the spreadability of the film on the buccal mucosa. They help in achieving better intimate contact and drug absorption. Polysorbate 80, sodium lauryl sulfate, and lecithin are common surfactants used in FDBFs [31].

pH Modifiers: pH modifiers are used to adjust and optimize the pH of the film to match the physiological conditions of the buccal cavity. They can enhance drug stability and improve compatibility with the oral mucosa. Examples include citric acid, sodium citrate, and sodium bicarbonate [32].

Antioxidants/Preservatives: Antioxidants and preservatives are added to FDBFs to prevent oxidative degradation or microbial growth during storage. Common examples include ascorbic acid, sodium metabisulfite, and benzalkonium chloride [33].

Film Forming Agents: Apart from polymers, additional film-forming agents can be used to enhance the film-forming ability and mechanical properties of the formulation. These may include hydrocolloids like sodium alginate or natural gums like xanthan gum [34].

Classifications of Fast Dissolve Technology

Fast-dissolve technologies can be divided in to three broad following groups shown in fig. 1[35]

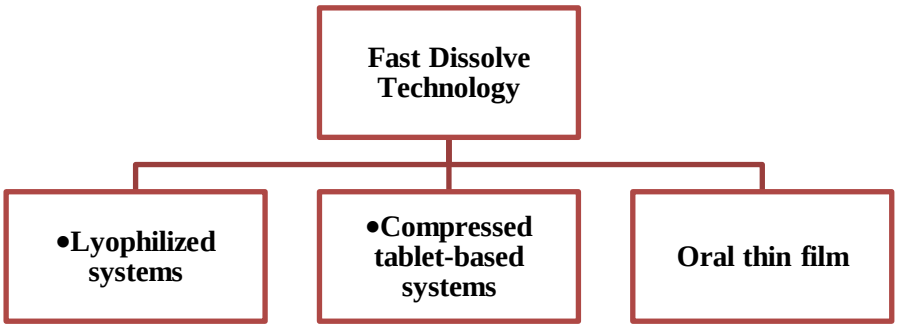


Fig. 1: Classifications of Fast Dissolve Technology

The lyophilized systems: This approach includes forming tablet-shaped units from a suspension or solution of a medicine and other structural excipients using a mould or blister pack, which is then placed in a container. Each of the units or tablets is frozen and lyophilized in the pack or mould after which it is removed. The resultant units have a very high porosity, which allows for quick water or saliva penetration as well as disintegration at a very fast rate [36].

Compressed tablet-based systems: This method is manufactured using normal tablet technology, which involves the direct compression of excipients. According on the manner of manufacturing, various degrees of hardness and friability are present in different tablet technologies. Fast-dissolve tablets disintegrate at a faster rate than ordinary tablets because they are made with water-soluble excipients, super-disintegrants, or effervescent components, which enable water to penetrate into the core of the tablet more quickly than standard tablets [37].

Oral thin film: Oral wafers are another name for this product. In the last several years, oral thin films have emerged in the confectionary and oral care industries in the shape of breath strips, among other applications. These are an innovative and well recognized manner of providing vitamins and personal care goods that customers have come to expect. Such systems make use of a range of hydrophilic polymers to form a film with a thickness ranging from 50 to 200 mm [38].

Manufacturing methods of Buccal film

Buccal film formulation is mainly prepared by following methods.

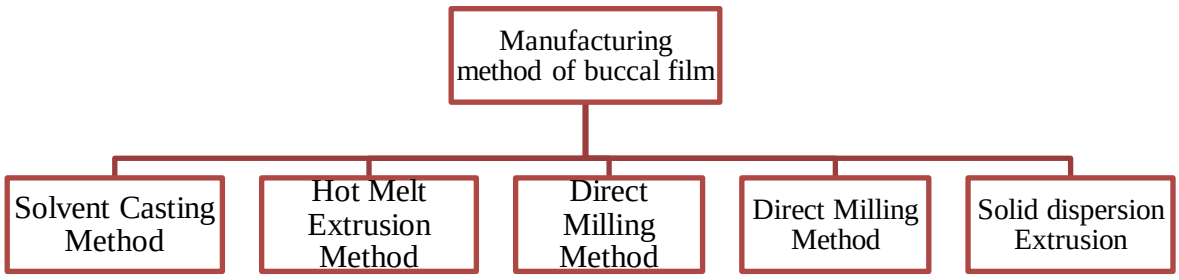


Fig. 2: Methods of manufacturing Buccal Film

Solvent Casting Method: Solvent casting is a technique in which a specified amount of polymer is introduced and dissolved in distilled water. A little amount of the active medicinal component has been added to this solution. The plasticizer is added to the solution and well mixed. The solution is then cast onto a Petri plate and dried at 400 degrees Celsius in a hot air oven. After drying, cut it out of the petri plate with a razor blade and place it in a desiccator for 24 hours to complete the drying process. From this point on, cut to the desired size and form. The following are the steps involved in the Solvent Casting Method [39]

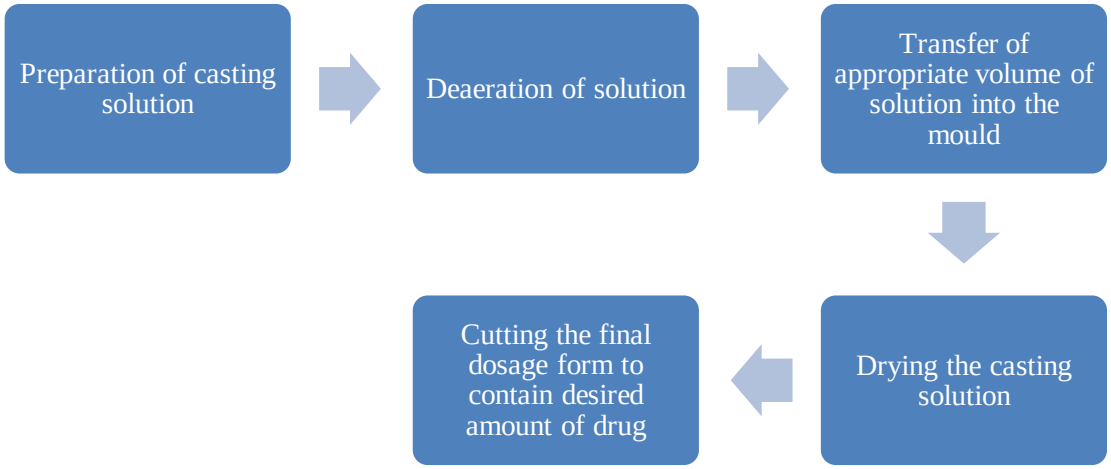


Fig. 3: Flow diagram of steps involved in solvent casting method

Hot Melt Extrusion Method: - The hot melt extrusion process involves melting a combination of the medication and additional excipients. The material is then pushed through an aperture to produce a more homogeneous substance that may be formed into various forms such as granules, tablets, or films. It is used in the delivery of drugs via the skin. The following are the steps involved in the Hot Melt Extrusion Method: -[40]

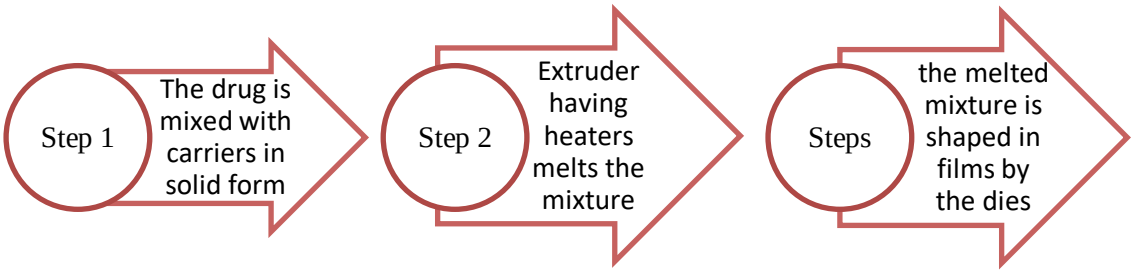


Fig.4: Flow diagram of steps involved in Hot melt extrusion methods

Various Advantages of hot melt extrusion method like, Fewer operation units, better content uniformity and anhydrous process. Some disadvantages are also observed like, stability problem for thermolabile compounds, flow properties of polymer are important to processing and limited numbers of polymers are available for this method [41].

Direct Milling Method: - This approach does not need the use of any solvents. Direct milling or kneading are used to combine the medicine and excipients in the absence of a liquid, resulting in a uniform mixture. In order to acquire the desired thickness, the resultant material is next wound around the released-liner rollers. This procedure is commonly recommended since there is no likelihood of leftover solvent and there is no link with any solvent-related health issues with this method.[42]

Semi- Solid Casting: The following steps were followed in the semi- solid casting method as shown in Figure No.9 [43]

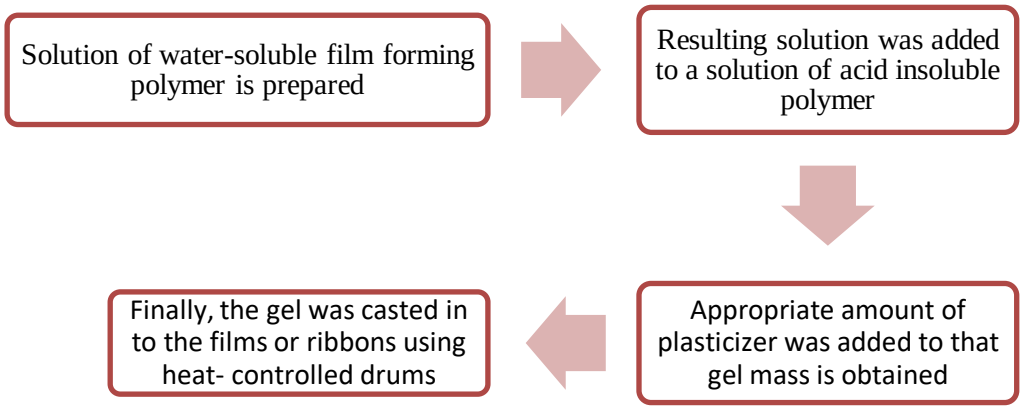
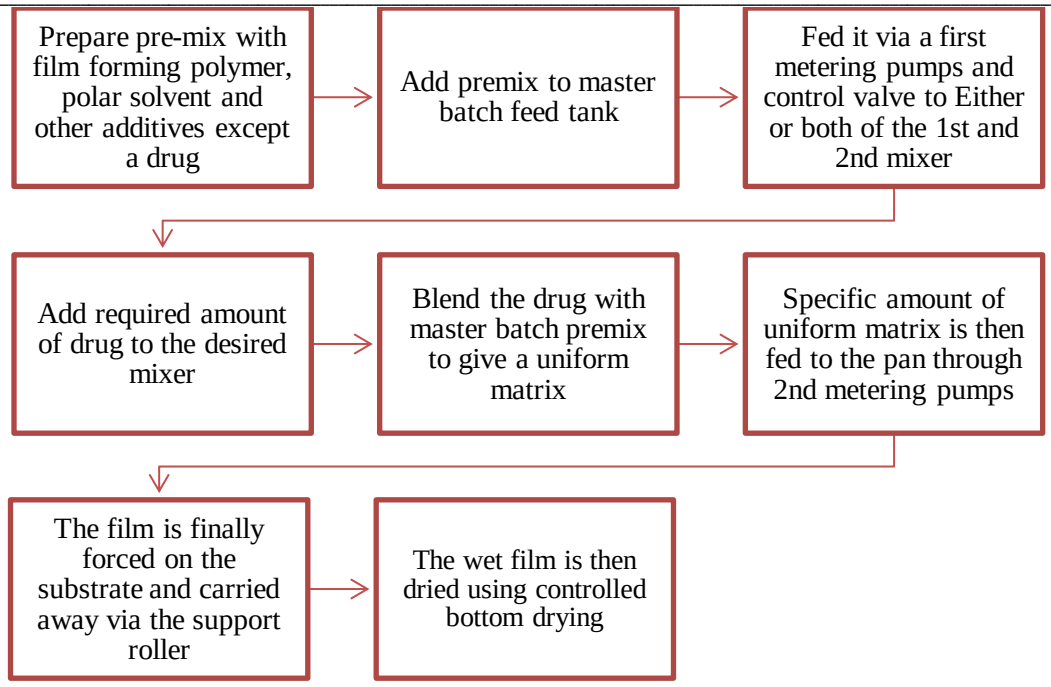


Fig.5: Flow diagram of steps involved in Semi- Solid Casting methods

Solid Dispersion Extrusion: - Fig.6 is shown the process of Solid Dispersion Extrusion[44]

Fig.6: The process of Solid Dispersion Extrusion.

Rolling Method: Following steps are taken for rolling method, shown in **Fig.6**[45]



Evaluation of Buccal Fast Dissolving Film: Following evaluation parameters are subjected to evaluation of fast dissolving film.

Weigh variation of Films: Mouths dissolving oral films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper number of excipients and API.[46]

Thickness of Films: By using micrometer screw gauge, the thickness of the film was measured at five different places; an average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.[47]

Folding Endurance: Folding endurance is measured by manual repeated folding of film at same place till it broke. The number of times the film is folded without breaking is known as the folding endurance value [48].

Tensile strength: Tensile strength is a maximum stress applied to a point at which the strip specimen breaks. It is calculated by applied load at rupture divided by the cross-sectional area of the strip as given in the following equation:[49]

$$\textbf{Tensile strength} = \frac{\textit{Load at failure}}{\textit{film}\ \textbf{thickness} \times \textit{film width}} \textbf{X100}\ldots\ldots\textbf{(Eq.1)}$$

Percent Elongation: When stress is applied to a film sample it stretches and this is referred as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally, elongation of film increases as the plasticizer content increases [50].

$$\%\ \textbf{Elongation} = \frac{\textbf{Increase in length}}{\textbf{Initial length of film}} \boldsymbol{X100}\ldots\ldots(\boldsymbol{Eq.2})$$

Drug content uniformity: This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%.[51]

Surface pH: The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done. [52]

***In vitro* disintegration test:** Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast-dissolving film, the time of disintegration should be in range of 5-30s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study Disintegration time. In another method, the

disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates.

Dissolution test: Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times, the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed**.** [53]

Stability Testing: Stability measurement is done by storing the of oral strip were stored under controlled conditions of 25ºC/60% RH as well as 40°C/75% over a period of 12 months in stability chamber according to the ICH guideline. During storage period various evaluating parameter like thickness, morphological properties, tensile strength, water content and dissolution behavior are checked.[54]

Marketed product of FDBFs[55-60]

There are several marketed products of fast dissolving buccal films (FDBFs) available in the market. Here are a few examples:

Table 2: Marketed Product of FDBES

S.No.	Name of product	Active API	Company name	Type of product	Use
1.	Suboxone	buprenorphine and naloxone	Indivior Inc.	Sublingual Film	To treat dependence on opioid (narcotic) drugs
2.	Onsolis	fentanyl citrate	Bio Delivery Sciences International) Inc	Buccal Film	cancer pain
3.	Zuplenz	ondansetron	Galena Biopharma Inc.	Oral Soluble Film	prevention of chemotherapy-induced nausea and vomiting
4.	Sancuso	granisetron	ProStrakan Ltd.	Transdermal Film	prevention of chemotherapy-induced and postoperative nausea and vomiting.
5.	Fentanyl	Fentanyl	Teva Pharmaceutical Industries Ltd	Buccal Film	to treat severe pain related to surgery or complex pain conditions.
6.	Riluzole	Riluzole	Zydus Cadila Healthcare Ltd	Oral Disintegrating Film	to treat amyotrophic lateral sclerosis
7.	Ondansetron	Ondansetron	Teva Pharmaceutical Industries Ltd.	Oral Soluble Film	empiric treatment of nausea and vomiting
8.	Granisetron	Granisetron	ProStrakan Ltd.	Transmucosal Film	to prevent nausea and vomiting caused by cancer chemotherapy and radiation therapy
9	Olanzapine	Olanzapine	Dr. Reddy's Laboratories Ltd.	Orally Disintegrating Film	helps to manage symptoms of mental health conditions
10	Rizatriptan	Rizatriptan	Mylan N.V.	Oral Disintegrating Film	to treat the symptoms of migraine headaches
11.	Diclofenac Sodium	Diclofenac Sodium	Dexcel Pharma Ltd	Buccal Film	treatment of pain and inflammation.

Future prospective

Fast dissolving buccal films (FDBFs) have emerged as a promising drug delivery system with several advantages, including ease of administration, improved patient compliance, rapid drug dissolution, and potential for enhanced bioavailability [61]. The future prospects of FDBFs involve advancements in formulation techniques by continuously exploring innovative formulation techniques to enhance the properties of FDBFs. This includes the use of different polymers, excipients, and additives to optimize film integrity, drug release, and mucoadhesive properties[62]. Novel manufacturing methods such as hot-melt extrusion, inkjet printing, and electrospinning may also be employed to improve film quality and reproducibility. Now days, recent advancements have been showing in incorporation of nanotechnology in FDBFs holds promise for improved drug delivery [63]. Nanostructured films, such as nanofibrous or nanoparticle-loaded films, can enhance drug solubility, stability, and permeability. Nanocarriers may also be utilized to encapsulate and deliver a wide range of drugs, including poorly soluble compounds and biologics [64]. FDBFs can be designed to deliver multiple drugs simultaneously or sequentially, allowing for combination therapies in a single dosage form. This opens up possibilities for personalized medicine, where different drugs or dosages can be tailored to individual patient needs [65]. Combination FDBFs could be particularly beneficial in the treatment of complex diseases or conditions that require the synergistic action of multiple drugs. FDBDs have also been used to deliver the Targeted and controlled drug delivery. Future FDBFs may incorporate targeting ligands or stimuli-responsive systems to achieve site-specific drug delivery[66]. This can enable selective drug release in specific regions of the oral cavity or target tissues, improving therapeutic efficacy and minimizing systemic side effects. The role of FDBFs for incorporation of theranostic capabilities in which combine therapeutic agents with diagnostic functionalities, enabling simultaneous therapy and monitoring of disease progression[67]. By incorporating imaging agents or biomarkers into the film formulation, FDBFs can provide real-time monitoring of drug release, drug localization, and disease response, thereby facilitating personalized treatment regimens. FDBFs focus on focus on patient-centric design, considering factors such as taste masking, ease of administration, and aesthetic appeal[69]. Efforts to improve the taste, appearance, and texture of FDBFs can enhance patient acceptance and compliance, particularly for paediatric and geriatric populations[70]. The integration of FDBFs with digital health technologies, such as smart sensors or electronic monitoring systems, can enable real-time tracking of medication adherence and provide feedback to patients and healthcare providers. These technologies can enhance treatment outcomes, support medication management, and enable personalized therapy[71-72].

Summary and Conclusion

Fst dissolving buccal films (FDBFs) hold significant promise as a drug delivery system, offering advantages such as ease of administration, improved patient compliance, rapid drug dissolution, and potential for enhanced bioavailability. The future prospects of FDBFs are characterized by ongoing advancements in formulation techniques, expanding applications, and the incorporation of novel technologies.

Future developments in FDBFs include improved formulation techniques, such as the use of different polymers, excipients, and additives, as well as the exploration of novel manufacturing methods like hot-melt extrusion, inkjet printing, and electrospinning. The integration of nanotechnology in FDBFs is also being explored, with a focus on nanostructured films and nanocarriers to enhance drug solubility, stability, and permeability.

Combination therapies within FDBFs are anticipated, enabling the simultaneous or sequential delivery of multiple drugs, leading to personalized treatment regimens. Additionally, FDBFs may incorporate targeted and controlled drug delivery mechanisms, allowing for site-specific drug release through targeting ligands or stimuli-responsive systems.

The incorporation of theranostic capabilities in FDBFs, which combine therapeutic agents with diagnostic functionalities, opens up opportunities for real-time monitoring of drug release, drug localization, and disease response. Patient-centric design considerations, including taste masking, ease of administration, and aesthetic appeal, are also expected to drive future developments in FDBFs, particularly for pediatric and geriatric populations.

Lastly, the integration of FDBFs with digital health technologies, such as smart sensors or electronic monitoring systems, has the potential to revolutionize medication management by enabling real-time tracking of adherence and providing feedback to patients and healthcare providers.

Overall, the future of fast dissolving buccal films is promising, with ongoing research and development focusing on improving formulation techniques, expanding applications, and incorporating novel technologies. These advancements have the potential to enhance drug delivery efficacy, patient compliance, and personalized therapy, ultimately improving patient outcomes.

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