A REVIEW OF ORODISPERSIBLE FILMS FOR ENHANCED DRUG DELIVERY

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This review article provides a comprehensive overview of orodispersible films as a versatile drug delivery system. Orodispersible films, also known as buccal films, offer several advantages over traditional oral dosage forms, particularly for patients who have difficulty swallowing, such as children, the elderly, and those with dysphagia. These films rapidly disintegrate in the oral cavity, allowing for easy administration and improved patient compliance. The review discusses the types of buccal films, including flash release, mucoadhesive melt-away, and mucoadhesive sustained-release films, as well as the key factors influencing their development and performance. It also highlights the various drugs that are suitable candidates for inclusion into orodispersible films, including those with low bioavailability, first-pass metabolism, and local effects. The review emphasizes the growing interest in this technology and its potential for addressing the challenges associated with traditional oral drug delivery.

Keywords: orodispersible films, drug delivery, patient compliance, rapid disintegration, mucoadhesion

INTRODUCTION

The use of the lingual route for drug administration is often chosen due to several benefits, such as ease of self-administration, ease of ingestion, patient compliance and many other advantages.[1] Both types of dosage forms, solid (*e.g*., capsules, pills, films *etc*.) and liquid (including syrups, emulsions, elixirs, and other compositions), offer various options. Solid forms ensure precise drug delivery post-swallowing, and they maintain their integrity under specific conditions. Despite numerous advantages, this administration route also has its drawbacks. One significant disadvantage is swallowing difficulty and chewing, particularly in children, the elderly, individuals with dysphagia, and those with throat disorders. Individuals in these groups often experience fear of choking when taking medication in these forms. To address these challenges, various rapidly dispersible formulations have been introduced.

Rapidly dispersible systems are developed based on the principle of “rapid disintegration”. Effervescent and disintegrating agents are incorporated to ensure the dissolution in the mouth. Due to patient compliance and ease of administration, this type of systems is gaining attention and marketability. Designed to disintegrate rapidly, *i.e.* within seconds in the mouth, this system eliminates the water needs. Orally administered thin films for drug delivery present a preferable alternative, which address the drawbacks of conventional dosage forms, including the choking risk and difficulties in swallowing. These films rapidly disintegrate, offering a swift solution. Additionally, challenges related to the interference of enzymes and stomach pH with drug absorption and metabolism can be mitigated through the use of rapidly dispersible films.[2] The per-oral quick-dissolving dosage form is placed on the tongue's surface, where it remains for a few seconds before dispersing or dissolving to release the active drug. This innovative approach offers various advantages in the development of drug delivery systems, including improvements in stability, bioavailability, solubility profiles, and half-life of the active drug.[3]

The goal of the latest developments in new drug delivery systems (NDDS) has been to improve medication safety and efficacy by creating a dosage form that is easier to administer and has higher patient compliance. Oral drug delivery modifications lead to the evolution of dosage forms, which start with standard solid dosage forms and progress to controlled/sustained release tablets/capsules, oral dispersible tablets, and ultimately buccal films. Buccal films represent a form of drug administration that is suitable for both the general public and especially for certain age groups that

have trouble swallowing, since they dissolve or disintegrate in the oral cavity without the need of water.[4]

It is worth noting that the oral mucosa exhibits varying degrees of permeability across different regions, the sublingual area demonstrating the highest permeability, followed by the buccal and palatal regions, due to differences in thickness and keratinization levels.[10] To transport the medication systemically through oral films, the films combine the medicine with specific oral mucosal penetration enhancers. Drugs that are absorbed through the oral mucosa bypass the gastrointestinal tract and the liver's first-pass metabolism, entering the systemic circulation directly. This is because the oral mucosa is rich in capillaries.[5] As a result, drugs with low oral bioavailability and causing intense hepatic metabolism are easily absorbed and act quickly, and are administered in a more convenient manner, compared to parenteral administration of drugs. Passive drug delivery through the oral mucosa primarily occurs via transcellular and paracellular routes. Hydrophilic drugs traverse intercellular spaces and cytoplasm due to their hydrophilic properties, while lipophilic drugs penetrate the cell membrane due to their lipophilicity.[10] This drug administration form thus provides better patient compliance, along with a quicker onset time and increased bioavailability.[5]

Orodispersible films present an exciting opportunity for both fundamental research and industrial applications, particularly with the integration of natural polymers. Natural polymers, such as cellulose, pullulan, chitosan, and sodium alginate, are increasingly employed in film formulations due to their biocompatibility, biodegradability, and suitability in controlled release systems. These polymers offer unique advantages in enhancing film flexibility, tensile strength, and patient compliance, while also addressing environmental sustainability. In industrial settings, these polymers facilitate scalable manufacturing processes, providing cost-effective, safe, and regulatory-compliant solutions for the production of orodispersible films. The use of natural polymers aligns with evolving industry trends that prioritize sustainable and patient-friendly drug delivery systems, reinforcing the relevance of natural materials in advancing orodispersible film technology.

TYPES OF RAPIDLY DISPERSIBLE DRUG SYSTEMS

Although the oral route for drug administration remains the primary one, lately, the buccal route has emerged as a promising alternative, as it offers a number of advantages. Buccal films are specifically designed with mucoadhesive properties. These films often incorporate permeation enhancers to boost drug bioavailability. Drawing from available literature, the buccal epithelium emerges as a favorable pathway for the administration of various drugs. This results in ongoing clinical trials, indicating a growing interest in registering and commercializing the first biologic product in the form of a buccal film. Numerous researchers engaged in instant release product studies are directing their attention toward “oral strip technology”. According to these researchers, oral strips offer notable advantages, particularly for population groups facing difficulties in swallowing. This technology is suitable for both sustained release (SR) and instant release (IR) formulations of drugs. Thus, oral films are considered an alternative drug delivery system, particularly for drugs having issues related to bioavailability and first-pass effects.[8]

Fast dissolving oral dispersible tablets

The traditional approach involves directly compressing the excipients to create the delivery system. The manufacturing process may impact the system’s friability and hardness. Such systems are constructed with water-soluble substances and include a super-disintegrant/effervescent component, enabling rapid disintegration and improved water penetration into the core compared to simple/conventional units. It can accommodate a significant amount of drug medium and other taste-masking materials. However, a drawback is its longer disintegration time compared to other rapidly dispersible systems. Many branded firms and generic pharmaceutical corporations utilize loose compression techniques in constructing these systems.

Thin oral films/wafers

Thin oral films, also known as ‘wafers’ in recent literature, consist of flat films recommended for placement in the oral cavity. Although this class emerged only a few years ago, it is currently gaining increased attention from manufacturers interested in fast-dissolving system development. Some organizations engaged in the development of transdermal delivery systems have employed a similar

technology to produce thin oral films. At present, thin oral films have gained widespread popularity and recognition for delivering the active constituents of over-the-counter products as well as some prescription medications. Hydrophilic polymers are utilized to manufacture such films. These films contain soluble or insoluble compounds and some taste-masked active ingredients. After formation, the resulting large, thin sheets are further cut into films with pharmaceutically suitable and desired patterns (50-200 mm).[11]

Lyophilized systems

The production process of such systems involves pouring liquid mixtures containing the drug into designated molds to create various tablet-shaped fragments. Subsequently, these fragments are allowed to freeze and then undergo lyophilization. Thanks to their highly porous nature, these fragments can rapidly disintegrate and experience increased water or saliva penetration. The dose handling capability in such systems varies depending on the nature of the active drug, whether it is soluble or insoluble. Moreover, taste masking agents can also be incorporated.[12]

Buccal films

Buccal films, resembling postage stamps in size and shape, are exceptionally thin films placed on the tongue, where they quickly hydrate to release the drug. These films are approved in USA and Japan under prescription. It appears that buccal films will dominate the market over other dosage forms containing the same active drugs. Buccal adhesive films represent a novel drug delivery system crafted using mucoadhesive polymers. Compared to adhesive tablets and oral gels, buccal films are preferred on the mucosa due to their flexibility, comfort, and relatively prolonged residence time. Additionally, buccal films have the ability to protect wound surfaces, thereby reducing pain and enhancing the effectiveness of oral disease treatment. Bi-layer films offer the advantage of serving as carriers for more than one drug simultaneously. Utilizing bi-layer films as a drug delivery system provides flexibility and adaptability, allowing for the incorporation of two drugs in separate layers. This approach offers several benefits, such as the ability to develop one layer for immediate release, ensuring a rapid onset of action. Meanwhile, the second layer can function as a sustained release layer, providing controlled and prolonged release of the drugs.

Fast-dissolving buccal films were developed by using glycerin as a plasticizer and maltodextrins, and *in-vitro* evaluation was conducted. The results indicated a concentration range of glycerin to the polymer 16-20% w/w yielded the most suitable composition of the films. In this selected formulation, the piroxicam was used with microcrystalline cellulose that was used as a carrier. The study's conclusions showed that although these particular ingredients made the films less flexible, they still had an excellent drug loading capacity of 25 mg per 6 cm^2 area.[9]

Types of buccal films

Buccal films can be classified into three distinct types based on their release mechanisms and manufacturing methods: flash-release films, mucoadhesive melt-away films, and mucoadhesive sustained-release films. Each type offers unique characteristics and applications.[6]

Flash-release films are typically single-layered and covering a small area (2-8 cm^2). They are placed on the tongue and disintegrate within 60 seconds, which makes them suitable for both local and systemic effects.

Mucoadhesive melt-away films may be single or multi-layered, they adhere to the buccal mucosa and disintegrate in a few minutes. They are generally used for applications where a slightly prolonged release is desired.

Mucoadhesive sustained-release films are composed of multiple layers, and cover a smaller area (2-4 cm^2). These films use non-dissolvable polymers to release the drug over an extended period (up to 8-10 hours), providing a controlled, sustained effect in the buccal cavity.

COMPOSITION OF BUCCAL FILMS

Buccal films disintegrate rapidly in the oral cavity. They are formulated as sustained release mucoadhesive films, facilitating drug absorption through the oral mucosa of the mouth, pharynx, and esophagus. The area of thin quickly dissolvable films ranges from 1-20 cm^2, depending on the dose and drug loading in the film. The recommended single dose for uploading is less than 30 mg. Key

formulation considerations, such as the choice of polymer or plasticizer, play an important role in influencing the mechanical properties of the films.[13]

Film-forming polymers

There is a diverse array of polymers available for the manufacture of rapidly dissolvable films. The choice of these polymers in the formulation depends on the desired characteristics of the film, with the option to select polymers individually or in combination with others.

The type and concentration of the polymer in the buccal film formulation play an important role. It is essential for the resulting film to possess the required durability and rigidity. On the other hand, a rapidly dissolvable film must be capable of swift disintegration to release the drug after oral placement. This process is crucial for achieving effective drug delivery at the intended site. Thus, determining the appropriate quantity of the polymer in the formulation is a critical stage in the production of films, as the dissolution is directly influenced by the polymer amount. The most frequently used film forming polymers include pullulan, gelatin, pectin, hydroxypropyl methylcellulose, carboxymethyl cellulose (CMC), sodium carboxymethyl cellulose (NaCMC), hydroxyethyl cellulose (HEC), sodium alginate *etc*.[26,27] Some of them are presented below.

Pullulan

Pullulan is a natural polysaccharide, its composition involves three glucose molecules and maltotriose units. The recurring maltotriose units contribute to its structural flexibility and amorphous characteristics. This white, tasteless powder initiates decomposition at 250 °C. Renowned for its adhesive, binding and film-forming properties, pullulan creates clear solutions in alkaline solutions and water, but is not soluble in all organic solvents.[21]

Gelatin

Gelatin is a protein derived from collagen. The primary source of gelatin is typically animal collagen, obtained from the bones and hides of cattle. There are two main types of gelatin. Type A is derived from acid-treated animal collagen, often sourced from pig skins, where the acid treatment breaks down the collagen into gelatin. Type B gelatin is obtained by subjecting animal collagen, usually from cattle bones, to an alkaline treatment. The stability of gelatin is influenced by its amino acid content, with higher levels correlating to increased stability. The film-forming ability of gelatin is associated with its molecular weight, where a higher molecular weight corresponds to an enhanced film-forming capability. Gelatin provides a smooth mouth feel and serves as an excellent carrier for flavors, displaying rapid dissolution characteristics.[22]

Sodium alginate

Sodium alginate serves as a dietary fiber source and is the salt form of alginate, boasting greater water solubility than its parent compound. Alginate possesses distinctive colloidal properties, acting as a constituent in coatings and polymer-containing films with various functions, such as suspending, gel-producing, emulsion stabilizing, thickening, and film-forming. Characterized by a hydrophilic nature, sodium alginate exhibits notable gelling capacity and can create robust films. The mixture of starch and alginate enhances the mechanical properties of the films.[23]

Chitosan

Chitosan has a glycopyranose ring in its structure, leading to the formation of a viscous polymer material that appears as porous. The films produced with chitosan exhibit uniform thickness, compactness, and cohesion.[24]

Hydroxypropyl methylcellulose

This is a cellulose derivative, consisting in methylated hydroxypropyl cellulose. Hydroxypropyl methylcellulose (HPMC) possesses outstanding acceptability and demonstrates excellent film-forming abilities. In an aqueous solution, HPMC yields flexible and transparent films that exhibit resistance to moisture and environmental factors. HPMC is available in various grades, with lower viscosity grades, such as E3, E5, and E15, specifically utilized for film formation purposes.[25]

Polyvinyl alcohol

Polyvinyl alcohol (PVA) is a synthetic polymer made from vinyl acetate polymerization; after polymerization, the acetate group is partially or completely hydrolyzed. It is water-soluble, forming a clear, colorless solution. It has good film-forming properties. PVA films are flexible, have good oxygen barrier properties and are strong. PVA is used in the pharmaceutical industry for coating tablets and as a component in controlled-release drug formulations. PVA is considered biodegradable under certain conditions, making it environmentally friendly.[26]

Polyvinylpyrollidone

Polyvinylpyrrolidone (PVP) is a synthetic polymer that belongs to the class of polyvinyl polymers. PVP is composed of repeating vinyl pyrollidone monomer and is water-soluble. The monomer unit has a lactam structure. PVP is highly soluble in water and other polar solvents, which makes it useful in various formulations. PVP has hygroscopic properties. PVP is commonly used in the pharmaceutical industry as a binder, film-former, and disintegrating agent in tablet formulations. PVP's ability to form films makes it valuable in applications where a thin, uniform coating is desired. This is particularly relevant in pharmaceutical and cosmetic formulations.

Active pharmaceutical ingredients (APIs)

In cases of different pathological complexities, there is a demand for the rapid release of the drug for swift relief. This urgency is particularly important in scenarios like migraine attacks, where a quick clinical response is desired. Thus, researchers have directed their attention toward the buccal cavity for the developing fast dissolving and mucoadhesive buccal systems for drug delivery, aiming to deliver various active pharmaceutical ingredients (APIs), while avoiding the potential hazards associated with the gastrointestinal tract (GIT).[7] Thin oral dissolving films have the capability to deliver different active pharmaceuticals. This type of systems makes possible the absorption and delivery of numerous drugs, encompassing treatments for conditions such as fungal infections, colds, coughs, anxiety, cardiovascular issues, throat inflammation, erectile dysfunction, severe allergic reactions, asthma, gastrointestinal complications, nausea, and certain central nervous system disorders. Most of the drugs which are potent and have low therapeutic dose, such as antihistamine, antitussive, antiepileptic and expectorants, can be formulated as buccal drug delivery systems. Moreover, drugs that cause gastrointestinal disturbance are good candidates for inclusion into oral films.[7] Additionally, film strips can incorporate caffeine, snoring aids, multivitamins, and sleep aids.

A critical consideration is dose: as a result of the restricted loading capacity of the films, drugs characterized by lower doses and lower molecular weights are generally preferred. This results in a successful integration of drug content ranging from 5 to 30% (w/w) within these films. Also, potential drugs under consideration must demonstrate favorable solubility and stability profiles in both aqueous environments and saliva. Furthermore, drug should remain partially unionized at the pH of the buccal cavity and exhibit efficient permeation across the oral mucosal epithelial barrier.[14] Hydrophilic drugs are typically dissolved and incorporated into the films in fast-dissolving dosage forms. Whereas for hydrophobic drugs, they are dispersed within the polymeric matrix of the film. In this process, drug molecules can undergo milling, encapsulation into nanoparticles and micronization to enhance the drug release profile in the films, thereby the solubility of the drug increases.[15] For drugs that are sparingly soluble in water, the incorporation into buccal films is still feasible by utilizing their salts or forming complexes. Moreover, even drugs with limited or no absorption through the oral mucosa can be considered as viable candidates, as their rapid dissolution in the mouth facilitates swift absorption through the gastrointestinal tract.

Surfactants

Surfactants operate on the principle of solubilizing the components of a formulation, inducing wetting, or making the compound available for dispersion. In the formulation pattern, the film is designed to dissolve rapidly, often within a few seconds, facilitating the swift release of the pharmaceutical agent. Commonly used surfactants include Tweens, sodium lauryl sulfate (SLS), propylene glycol (PEG), and benzalkonium chloride. Polaxamer 407 is a significant type of surfactant, employed for the purpose of dispersing, wetting, and solubilizing materials.

Plasticizers

The compatibility between the polymer and plasticizer is a determining factor in the selection of the plasticizer. Additionally, the type of solvent is a critical consideration before choosing the plasticizer. This choice contributes to making the film less brittle and more tensile. The plasticizer typically constitutes 0-20% w/v of the collective weight of the dried polymeric material in a film. Examples of these components include propylene glycol, glycerol, PEG-400, PEG-600, PEG-2000, sorbitol and castor oil. Their incorporation offers the advantage of preventing issues such as cracking, splitting, and peeling of the films.

Sweeteners

APIs with unsweetened taste may be unpleasant, especially for pediatric patients. Therefore, taste masking becomes essential before incorporating such agents into the formulation. Various methods are employed to make the formulation's taste agreeable.

Sweeteners are utilized in concentrations ranging from 3% to 6% w/w and can be either natural or artificial. These masking agents can be used individually or in combination based on specific needs. Sweeteners play an important role in the formulations of both pharmaceuticals and nutraceuticals, as they are designed to be dissolved in the oral cavity. Commonly used sweeteners are glucose, maltose and fructose. Among these, fructose is the most frequently utilized sweetener due to its sweeter taste compared to mannitol and sorbitol. Additionally, sweeteners contribute to a flavorful sensation in the mouth and a cooling effect. Artificial sweeteners have gained significant popularity and marketability and are categorized into two generations. Acesulfame-K falls under generation I and is 200 times sweeter than other sweeteners, while sucralose boasts a sweetness level of 600 times. In generation II, Neotame possesses a sweetening potential of 2000, while Alitame is impressively 8000 times sweeter than sucrose.

Flavors

Approved flavors by the US FDA can be incorporated into a composition. This includes sour fruity flavors, potent mint, and sweet flavors commonly used in confections. To mask the taste of a composite, the required quantity is determined by considering the type and strength of the flavoring constituent.

Components for saliva secretion

To ensure the rapid disintegration of rapidly dissolvable films, it is essential to stimulate excess salivary discharge. In the production of these films, acidic elements serve as saliva stimulatory vehicles. Common components in this category include citric acid, lactic acid, ascorbic acid, malic acid and tartaric acid.

Colorants

To give a distinct appearance to a pharmaceutical form, a suitable colorant is added. A broad range of colorants, including C&FD and EU colors, as well as titanium dioxide and other pigments, are currently available in the market. Additionally, naturally occurring colors, such as well-known chlorophylls, carotenoids and curcumin are also viable options.

General recipes and features of buccal films are presented in Table 1 and Table 2, respectively.

Table 1
General formulation of rapidly dispersible thin oral films

Ingredient	Quantity %(w/w)
Water dissolvable polymers	45-50
Drug	5-30
Plasticizer	0-20
Sweetening agents	3-7
Saliva stimulants	2-5
Surfactant	q.s.

Table 2
Special features of buccal films

Thin films	Convenient dosing
Different size and shapes	Less or no need of water
Non-obstructive	No choking risk
Mucoadhesive	Taste of drugs can be masked
Rapid disintegration	Stable
Dissolve quickly	Better patient compliance

MANUFACTURING TECHNIQUES OF BUCCAL FILMS

Several methods are used for the preparation of buccal films, each with its advantages and limitations. The selection of the method for manufacturing the films generally depends on the requirements of the drug, the desired characteristics of the buccal film, and practical considerations. Some common methods for the preparation of buccal film are presented below.

Solvent casting technique

The solvent casting technique is commonly used in the formulation of buccal films. The polymeric solution containing the drug and other excipients is cast onto a substrate, followed by the evaporation of the solvent to form a thin film. This method allows for the production of flexible and uniform films that adhere to the buccal mucosa for drug release. Suitable polymers are chosen based on the desired properties of the buccal film. Then, the solvent or a mixture of solvents are selected that can dissolve the chosen polymers and other excipients effectively. The drug is dissolved in the solvent, and then mixed in the polymer solution to achieve a homogeneous mixture. Stirring or other mixing techniques may be employed to ensure uniformity. Then, the polymer solution is poured or spread onto a flat, inert substrate or casting surface. The substrate can be made of various materials, such as plastic, glass and steel. The solvent is allowed to evaporate at controlled temperature and humidity conditions. As the solvent evaporates, the polymers form a thin, flexible film on the substrate. Once the solvent has completely evaporated, the buccal film needs to be carefully peeled from the substrate. The resulting film should be flexible, uniform, and free of defects. Finally, the buccal films are cut into the desired size and shape, and packaged in appropriate materials to protect them from moisture and environmental factors.[17]

Semi-solid casting method

In this method, the combination of drugs, polymers, and excipients is dissolved harmoniously. Utilizing a magnetic stirrer, the mixture is homogenized and left undisturbed for a duration of 8 hours. Subsequently, the casting process is carried out using a Petri dish. The films produced are subjected to drying in a hot air oven set at a temperature range of 45-50 °C. Once dried, the films are peeled and trimmed to suitable sizes for characterization.[18]

Hot melt extrusion technique

This method involves the continuous extrusion of a molten mixture of drug, polymers, plasticizers, and other excipients to form a uniform and solid dosage form. The drug is combined with polymers, plasticizers, and other excipients in the required proportions. The mixture is then heated until it becomes a homogeneous molten mass. The molten mixture is fed into the extruder. The screw rotates to transport and compress the molten material through the barrel. For buccal film preparation, the die can be configured to produce a flat, ribbon-like structure. As the extrudate exits the die, it is rapidly cooled to solidify the molten mass into a solid film. This cooling process is crucial to maintain the desired film structure. Once the film is solidified, it is cut into the desired size and shape. Hot melt extrusion method is not common for the manufacture of films.

A variation of this method is solid dispersion extrusion. The prepared solid dispersion undergoes an extrusion process to generate a uniform mass. Through this solid dispersion extrusion process, Domperidone was transformed into an oral buccal film. The method involved the incorporation of PEG 400, HPMC E15 and beta-cyclodextrin.[18]

Spray coating technique

In the spray coating technique, the drug, polymer, and excipients are dissolved in a suitable solvent to yield a transparent solution. This solution is subsequently uniformly poured or sprayed onto a substrate, such as a Teflon sheet, Kraft paper, or glass. Following the drying process, the polymer is separated from the support, resulting in the formation of an oral film.[19]

Emulsion solvent evaporation technique

This method involves the formation of an emulsion, where a drug-polymer solution is emulsified in a continuous phase, followed by the evaporation of the solvent to form the film. The drug is mixed in the polymer solution to achieve a homogeneous mixture. An emulsion is formed by combining the drug-polymer solution (internal phase) with an external phase containing an emulsifying agent and a continuous phase (often water). A high-shear homogenizer or an ultrasonic homogenizer is used to create a stable emulsion. The emulsion is allowed to stand or gentle heat is applied to facilitate the evaporation of the solvent. As the solvent evaporates, a thin, flexible film is formed with the drug and polymer distributed throughout. Once the solvent has completely evaporated, the film is carefully peeled from the substrate.[20]

NATURAL POLYMER-BASED ORODISPERSIBLE FILMS

The development of orodispersible films using natural polymers has led to several promising formulations, with unique properties tailored to enhance drug delivery efficiency, patient compliance, and biocompatibility. Some key examples of such films are described below, along with their characteristics and *in vivo* or clinical study outcomes.

Pullulan-based films

Pullulan, a natural polysaccharide, is widely used in orodispersible films for its excellent film-forming properties, transparency, and biodegradability. Studies have shown that pullulan-based films enhance drug stability and disintegration speed, making them suitable for immediate-release formulations. Clinical evaluations have demonstrated their effectiveness in providing rapid drug absorption, particularly for pediatric and geriatric patients who have difficulty swallowing tablets.

Sodium alginate films

Known for its high biocompatibility and gel-forming ability, sodium alginate is frequently used in orodispersible film formulations. Its ability to form viscous solutions improves film flexibility and patient comfort. *In vivo* studies have indicated that alginate-based films maintain structural integrity in the oral cavity, while offering controlled drug release, particularly in buccal applications. Alginate's interaction with salivary ions further enhances the mucoadhesive properties, making it effective in localized oral treatments.

Chitosan films

Chitosan, derived from chitin, has been extensively evaluated for its mucoadhesive properties and permeability-enhancing effects in orodispersible films. Due to its positive charge at physiological pH, chitosan enhances the residence time of films on mucosal surfaces, promoting prolonged drug release. *In vivo* studies have shown that chitosan-based films are effective for drugs that benefit from sustained release, as the polymer interacts with mucosal tissues to extend drug absorption.

Pectin-based films

Pectin, a natural polysaccharide, is utilized for its ability to form gels in the presence of divalent cations. Pectin-based orodispersible films are typically soft and comfortable in the mouth, with *in-vivo* studies supporting their use in formulations requiring controlled release. Clinical trials on pectin films for buccal drug delivery have demonstrated favorable outcomes, showing improved drug bioavailability and patient compliance.

The versatility of natural polymers is useful in the development of orodispersible films and in enhancing their performance, underscoring the suitability of these materials for industrial-scale applications. Natural polymers not only improve film characteristics, but also align with patient-centric design, offering enhanced safety and efficacy for a broad range of pharmaceutical applications.

Examples of orodispersible films based on natural polymers, together with their characteristics, are tabulated in Table 3.

Table 3
Some orodispersible films with their key characteristics

Type of film	Polymer used	Drug	Key characteristics	*In vivo*/clinical findings
Pullulan-based film	Pullulan	Loratadine	Transparent, fast disintegration, high stability	Effective rapid absorption, patient-friendly for children
Sodium alginate film	Sodium alginate	Ibuprofen	Mucoadhesive, controlled release, flexible	Enhanced drug retention in oral cavity
Chitosan film	Chitosan	Acyclovir	Strong mucoadhesion, extended release, permeation-enhancing	Prolonged drug presence on mucosal surfaces
Pectin-based film	Pectin	Nicotine	Gel-forming, controlled release, soft texture	Improved bioavailability, effective for buccal delivery

Advantages and limitations of buccal films

Buccal films exhibit several outstanding characteristics. They are user friendly, offer convenient dosing, and can be easily labeled and packaged. The surface area of buccal films can extend up to 25 cm^2. Rapid hydration is essential for prompt disintegration in the mouth, ideally within 1-30 seconds, facilitating the release of the drug. These films should be designed to minimize or eliminate residue in the mouth after disintegration.

Buccal films are characterized by flexibility and easy transportability, compared to tablets, which are usually brittle, necessitating specialized packaging for storage and transportation. Buccal films offer precise dosing in the form of strips, when compared with liquid dosage form. They are particularly friendly for dysphagic patients, as no water is required for administration. The larger surface area of buccal films enables rapid wetting, allowing them to be consumed conveniently anywhere. Direct absorption of drugs through the vascularized buccal mucosa bypasses the hepatic metabolism, enhancing drug bioavailability. This is especially beneficial for drugs with extensive first-pass metabolism. The reduced hepatic metabolism results in lower doses, decreasing the likelihood of dose-related side effects. Buccal films are also commonly used to achieve local effects in the mouth to treat oral thrush or other oral ailments. Buccal films offer a practical solution for medicating mentally ill, disabled, or uncooperative patients, presenting a clinical advantage. Furthermore, buccal films can serve as cost-effective alternatives to buccal tablets. The manufacturing process of buccal films is economically efficient, resulting in reasonably priced end-products with clinical advantages.

Still, their development can pose some challenges. For example, loading drugs with higher doses into buccal films is quite difficult due to size limitations. A critical formulation factor for these films is ensuring content uniformity. The hygroscopic nature of some drugs may further complicate matters, requiring special packaging for safety and stability. The primary focus of the buccal film being to deliver the drug to the oral cavity, the drugs with bitter taste may affect the films' palatability. Additionally, the continuous secretion of saliva poses a potential obstacle, leading to dilution or loss of the drug and further limiting the feasibility of buccal film formulation.[16]

CONCLUSION

Orodispersible films have emerged as a versatile and patient-centric drug delivery system, offering a promising alternative to traditional oral dosage forms. This review has provided an overview of the various types of buccal films, including flash release, mucoadhesive melt-way, and mucoadhesive sustained-release formulations, along with the key factors influencing their development and performance. The rapid disintegration and dissolution of these films in the oral cavity eliminate the need for water intake, making them an attractive option for patient groups who have difficulty

swallowing, such as children, the elderly, and those with dysphagia. By bypassing the gastrointestinal tract and avoiding first-pass metabolism, orodispersible films can enhance the bioavailability of drugs with poor oral absorption, while also providing a more convenient and comfortable administration route. Due to these important advantages, orodispersible films have a promising future in the pharmaceutical industry.

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