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REVIEW ARTICLE

Oral disintegration films: applications and production methods

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Abstract The use of orally disintegrating films (ODF) as a vehicle for the release of active compounds has drawn attention due to the advantages such as ease of swallowing, precise dosage, low thickness, flexibility, greater comfort and acceptability by the patient in relation to oral tablets, for do not require water for administration, it is ideal for people with difficulty in swallowing. In this review, recent advances in ODFs, their applications and production methods will be presented. The production of ODFs uses polymers, plasticizers and active compounds. Among the compounds added to the film that can affect its properties, the polymer used has a strong influence on the disintegration time and on the controlled release of active principles. Polymers used for the production of oral films must be non-toxic, have good wettability and spreadability, and may be of synthetic or natural origin. Regarding the methods used in the production of ODFs, those currently used are solvent evaporation and hot extrusion. However, one of the great challenges for the production of oral films is the scale up, from laboratory to industrial scale, as factors such as heating, mixing speed and temperatures can lead to changes in film quality. Recently, ODFs have been developed as carriers of natural compounds such as vitamins, phenolic compounds, antioxidant and antimicrobial activity. Thus, it was found that orally disintegrating films are an alternative for the release of active compounds, different from those already existing, which justifies the growing interest in this type of film.

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Keywords Orodispersible films · Active compounds · Edible polymers · Methods of production · Applications

Abbreviations

ODF	Oral disintegrating films
HPMC	Hydroxypropyl methylcellulose
HPC	Hydroxypropylcellulose
CMC	Carboxymethylcellulose
HPMC	Hydroxypropylmethylcellulose
FDA	Food and Drug Administration

Introduction

Oral disintegrating films (ODF) are also called fast dissolving films, oral films, orodispersible films, among other designations. And it has been seen as a new technology developed for the oral administration of active compounds (Borges and De Carvalho 2015; Takeuchi et al. 2019). According to the FDA (food and drug administration), they are single or multilayer sheets, of suitable materials, designed to quickly release one or more active substances in the mouth, forming a fine suspension or solution in saliva without chewing or ingesting water. They are solid most advanced forms in terms of flexibility (Thakur et al. 2019; Musazzi et al. 2020).

Research on ODF has drawn attention in recent decades for its advantages over other pharmaceutical forms such as fast-dissolving tablets. Due to an easy release of active compounds, the development of these films has drawn the attention of the industrial sector as well. The first researches report that the development of ODFs focused on combating bad breath, and its evolution occurred through the incorporation of actives with the most diverse applications (Borges and De Carvalho 2015; Qin et al. 2019).

The films have a larger surface area and disintegrate easily and in a few seconds in the oral cavity, causing a quick release of the active ingredient. As the oral mucosa is highly vascularized, the active compound can be absorbed directly into the systemic circulation, resulting in rapid absorption and better bioavailability, avoiding first-pass metabolism (Kumar et al. 2017). The oral dissolution film formulation is composed of materials such as film-forming polymers, plasticizers, active compounds, sweetening agents, saliva stimulants, flavorings, dyes, surfactants, permeation enhancers and disintegrants (Thakur et al. 2019).

In people affected by functional and psychological dysphagia, the use of oral disintegration films has become attractive. These patients prefer orodispersible films rather than liquid dosage forms, as do pediatric patients (Scarpa et al. 2017a), geriatricians (Slavkova and Breitkreutz 2015), bedridden patients and people without access to water, once placed on the tongue, it quickly disperses into smaller pieces and can be easily swallowed (Thabet and Breitkreutz 2018).

Natural and synthetic polymers can be used in the production of films and can be elaborated in different compositions to achieve the desired properties of the product (Karki et al. 2016). The polymer is responsible for giving important characteristics to the films and its choice is the first step in the development of these materials, as characteristics such as good handling and high hydrophilicity to facilitate dissolution in the oral cavity are fundamental to the elaboration process (Tedesco et al. 2016).

Films can be prepared by conventional methods such as solvent evaporation and hot extrusion. Recently, however, tape-casting and printing technologies are being investigated in the preparation of orally disintegrating films (Buanz et al. 2015; Vuddanda et al. 2017). This review aims to address recent advances in orally disintegrating films, their applications and production methods in the food industry.

Oral disintegration films

Oral disintegrating films should be approximately 1 mm thick to facilitate application to the oral mucosa. They are composed of polymers, film formers, plasticizers and active compounds of interest. Other compounds can be added, such as flavoring, coloring and sweeteners for better consumer acceptance (Bala et al. 2013; Borges and De Carvalho 2015).

Orally disintegrating films can be classified depending on their functional or physical properties. They can be divided into three categories, which are orally disintegrating films, mucoadhesive films and adhesives, according to their mucoadhesion properties and release time of the active principles (Preis et al. 2015).

They are usually produced from soluble polymers with high hydrophilicity, presenting instantaneous release, and must dissolve in a maximum of 60 s (Bhattarai and Gupta 2016) easily administered by people with dysphagia, nausea and mental disorders as they are applied on the tongue (Bhattarai and Gupta 2016).

Mucoadhesive films are mainly produced with hydrophilic polymers, which increase in volume and allow interactions with mucin molecules in the oral mucosa (Morales and McConville 2011). They disintegrate in a few minutes, forming a gel, continuously releasing the drug over time, and are usually applied to the oral mucosa, adhering to the surface (Bhattarai and Gupta 2016).

Films such as "adhesives (adhesives)" adhere to the mucosa and remain for hours releasing the active compound (Jani and Patel 2014). After the release ends, the film must be removed (Jani and Patel 2014). These films are produced in multilayers, usually with insoluble or low-solubility polymers (Bhattarai and Gupta 2016).

Garcia (2016) presents another classification, where the author reports that orally disintegrating films can be classified as oral disintegrating films of rapid release, mucoadhesive and controlled. The main characteristics of this classification can be seen in Table 1.

Table 1 Characteristics of oral disintegration films *Source*: Garcia (2016)

Characteristics of ODFs			
Properties	Quick release ODFs	Mucoadhesive release ODFs	Controlled-release mucoadhesive ODFs
Area (cm^2)	2–8	2–7	2–4
Thickness (μm)	20–70	50–500	50–250
Structure	Single-layer	Single-layer/multilayer	Multilayer
Excipients	High solubility hydrophilic polymers	Soluble hydrophilic polymers	Low solubility/insoluble polymers
Application	Tongue (upper palate)	Gingival or buccal region	Gingival (another region of the oral cavity)
Disintegration time	Less than 60 s	In a few minutes	Maximum 8–10 h
Action location	Systemic or local	Systemic or local	Systemic or local

Pharmaceutical company Pfizer developed the first commercial oral film that was named "Listerine® pocket packsTM" for use as a mouthwash (Bala et al. 2013). The first oral film of therapeutic use, containing benzocaine as an active ingredient, to be used in the treatment of sore throat was Chloraseptic® (Bala et al. 2013). Several oral release films can be found commercially, as can be seen in Table 2.

Composition of oral disintegration films

Regardless of the classification, orally disintegrating films present a typical formulation with variation of some components and their concentrations according to the desired application. The formulation must be developed in a way that attracts the consumer, has a good physical appearance, masks the unpleasant taste and all excipients used are approved for use in oral dosage forms which are considered safe (listed as GRAS generally recognized as safe) (He et al. 2021).

The main components used in the production of orally disintegrating films are generally polymers, plasticizers and active compounds. Other ingredients can also be added, such as sweeteners, colorings, saliva stimulators, flavorings, stabilizing agents and thickeners (Singh et al. 2018b; Zhang et al. 2020), as shown in Table 3.

According to Singh et al. (2018a) other ingredients may be incorporated into orally disintegrating films in reduced amounts to impart desired properties to them. Plasticizers are considered to be ingredients of fundamental importance since they act by improving the flexibility and reducing the fragility of the films. The selection of the type of plasticizer used in orally disintegrating films will depend on the compatibility with the polymer and the type of solvent used (Kaur and Garg 2018).

Saliva-stimulating agents are generally acidic in nature, to stimulate saliva production in the oral cavity and promote film disintegration (Irfan et al. 2016). Citric acid, malic acid, ascorbic acid, and tartaric acid are generally considered saliva-stimulating agents and can be used alone or in combination (Irfan et al. 2016; Bala and Sharma 2018; Alhayali et al. 2019).

Table 3 Main compounds used in the production of oral disintegration films. *Source*: Singh et al. (2018a, b)

Component	Concentration
Active compound	5–30%
Water-soluble polymer	45%
Plasticizer	0–20%
Saliva stimulating agent	2–6%
Surfactant	q.s.*
Sweetening agents	3–6%
Flavor, Color	q.s.*

*Sufficient quantity

According to Dahmash et al. (2021) added sweeteners in the production of orally disintegrating films are especially important for the pediatric population. Sweetening agents can be of natural origins, such as glucose, fructose, dextrose, sucrose and isomaltose, or synthetic origins, such as acesulfame–k, sucralose and neotame (Irfan et al. 2016).

There are some difficulties in the development of ODF, the problems are related to its instability in environments with high relative humidity, the small dose of a drug that can be incorporated, due to its small size, low weight and thin thickness. Some active principles cannot be used for incorporation in these films, such as those that are unstable in oral pH and can irritate the oral mucosa (Irfan et al. 2016; Karki et al. 2016; Sharma et al. 2016a). Another limitation is related to the production technique, in the standardization of film thickness to ensure dose uniformity (Sharma et al. 2015).

Polymers used in the oral disintegration films

Several polymers can be used in the production of orally disintegrating films, which can be used alone or in the form of blends, according to the desired properties (Alhayali et al. 2019). In addition to helping the material's structure, polymers can also improve chemical, physical and microbiological stability, active ingredient bioavailability and consumer acceptance (Lam et al. 2014a).

Table 2 Examples of commercial oral films

Commercial name	Active principle	Functionality
Niquitin strips®	Nicotine	Help to stop smoking
Sumnusent®	Melatonin	Restores the natural sleep cycle
Gas-X®	Simethicone	Gas treatment
Sandoz®	Sildenafil	Restoration of erectile function
Triaminic thin strips®	Dextromethorphan and phenylephrine	Cough and cold
ZenTrip®	Meclizine hydrochloride	Treatment of nausea

Solubility in water is one of the main considerations for polymer selection in the production of orally disintegrating films. Several ingredients are needed for the production of these films, but the polymer is the main one, as it helps in the formation of the films (Alhayali et al. 2019). The choice of polymer for the production of the oral film is extremely important, as they are mainly responsible for characteristics such as drug release rate, mucoadhesive and mechanical properties (Karki et al. 2016).

Polymers of natural or synthetic origin, such as starch (Limpongsa and Jaipakdee 2020), chitosan (Verma et al. 2018), gelatin (Borges and De Carvalho 2015) and hydroxypropylmethylcellulose (Singh et al. 2018a) can be used in formulation of orally disintegrating films. Also, different compositions can be used to achieve the desired properties of the films (Karki et al. 2016).

A critical step is polymer selection for the development of oral film matrices, which can vary according to the profile of the target product. It is important when choosing the polymer to observe its affinity with the active compound of interest and the mechanical properties of the films must be considered, as the film must be strong enough to be handled and transported without being damaged, in addition to keeping the active compound stable. until its release (Borges and De Carvalho 2015).

Tedesco et al. (2017) produced oral disintegration films based on gelatin and hydroxypropyl methylcellulose incorporated with peanut skin extract, considered a residue from the peanut processing industry and a source of phenolic compounds. In this regard, its application in oral films (OFs), and thus in the delivery of compounds obtained from industrial waste can be interesting and may enable them to be incorporated into diet as a supplement of important compounds for health.

Hydroxypropyl methylcellulose (HPMC) and hydroxypropylcellulose (HPC) are polymers commonly used in film formulations (Tedesco et al. 2016; Singh et al. 2018a). In the study Tedesco et al. (2021) the production and characterization of oral films based on carboxymethylcellulose (CMC), hydroxypropylmethylcellulose (HPMC) and pregelatinized starch with incorporation of ethanolic extract of dehydrated acerola residue was carried out. The authors report that the addition of dehydrated acerola residue to the films led to a reduction in tensile strength and an increase in contact angle values; however, the surface pH of the films remained close to the oral pH (6.8).

Tedesco et al. (2016) evaluated gelatin-based and hydroxypropylmethylcellulose in different proportions (0:100; 25:75; 50:50; 75:25; 100:0) and observed that the increase in the hydroxypropylcellulose concentration caused a reduction in hydrophilicity and disintegration time and increased the mucoadhesiveness. Borges and Carvalho (2015) developed films of gelatin and hydrolyzed collagen added with propolis extract that proved to be good carriers of active components for release in the oral cavity.

Garcia et al. (2020) produced films of oral disintegration based on pre-gelatinized starch and gelatin with the incorporation of acerola powder and evaluated the effect of the concentration of macromolecules on the properties of the films. It was observed that the gelatin/starch ratio did not affect the antioxidant activity of the films, however, the inclusion of starch in the films increased its hydrophilicity and decreased the disintegration time.

Active compounds

Several classes of active compounds can be incorporated in orally disintegrating films, of natural or synthetic origin. According to Singh et al. (2018a) orally disintegrating films have the potential for the administration of several active compounds, however, due to the small size of OFDs, large doses are difficult to be incorporated, generally containing only 5–30% of the active compound.

Active compounds are added to give different functionalities to the films such as antioxidant and antimicrobial properties, among others. The studies available in the literature, mostly, report the incorporation of synthetic active compounds, such as the antidiabetic metformin hydrochloride (Haque and Sheela 2015), fluoxetine antihistamine (Chevala et al. 2015) and prednisone anti-inflammatory (Brniak et al. 2015). The amount of active compound added to films will depend on their size. Increasing the amount of active compound added leads to increased brittleness and longer disintegration times, which is an important point when selecting the active compound and dose per film. The highest dose available on the market today is 100 mg of Sildenafil. Palatability boosts adhesion, but the film limits the addition of excipients to mask the taste, even though the astringent or bitter taste of the active compound can be reduced or eliminated (Cilurzo et al. 2010, 2011).

In cases of excessively bitter active compounds, some flavorings can be used to improve or mask the flavor of the formulations (Hoffmann et al. 2011). Table 4 presents some examples of active ingredients incorporated in orally disintegrating (ODF) films, with most studies reporting the incorporation of synthetic active ingredients.

Mechanisms for absorbing active compounds

The delivery of active compounds can be performed through different regions in the oral cavity, which differ in terms of anatomy, permeability and ability to retain the distribution system for the desired period (Lai et al. 2018). The regions are (a) sublingual where the active compound is administered through the sublingual mucosa for systemic

Table 4 Examples of active ingredients incorporated in oral disintegration films

Active compound	Reference
Prednisolone	Brniak et al. (2015)
Fluoxetine	Chevala et al. (2015)
Tadalafil	Vuddanda et al. (2017)
Meloxicam	Song et al. (2018)
Ropinirole	Lai et al. (2018)
Acetylsalicylic acid	Qin et al. (2019)
Risperidone hydrochloride	Bharti et al. (2019)
Venlafaxine hydrochloride	Al-Mogherah et al. (2020)

circulation; (b) buccal where administration of the active compound for systemic circulation occurs through the oral mucosa, cheek lining and area between the gums and the upper and lower lips; and (c) periodontal for the local treatment of conditions in the oral cavity such as aphthous ulcers, mainly bacterial and fungal infections and periodontal disease (Lam et al. 2014b; Lai et al. 2018; Alaei and Omidian 2021).

The absorption of components and nutrients can be carried out in two ways, being transdermal and transmucosal. The transmucosal pathways are the most studied and include the pulmonary, gastrointestinal, vaginal, rectal, ocular and oral tissues, with the rectal, vaginal and ocular mucosa being the least accepted by patients, in addition to being mainly restricted to the release of the drug for local diseases (Alaei and Omidian 2021).

The absorption of active compounds is facilitated by the oral mucosa as it is a highly vascularized region. This absorption can occur either through the sublingual route (region under the tongue) or through the oral route (lateral region of the oral cavity), with the sublingual region being the most permeable (Kumar et al. 2017). The absorption of the compound in the oral cavity prevents its passage through the entire gastrointestinal tract, thus avoiding degradation by enzymatic action and pH variations and also preventing first-pass metabolism, ensuring greater stability of the component and increasing its bioavailability (Lai et al. 2018; Hua 2019).

The oral administration of actives is preferred due to its ease of administration, being easy to adapt and acceptability by the patient (Irfan et al. 2016). Oral disintegrating films, when administered orally (sublingually, buccally and palatal), prevent the degradation of the active ingredient by liver enzymes in the first-pass metabolism, which could lead to its elimination, in addition to not reaching the desired levels in therapeutic approaches (Takeuchi et al. 2019).

The delivery of active compounds through the oral mucosa, however, presents some challenges, such as the need to present a pleasant taste, the selective permeability of the oral mucosa and the prevention of active compounds from being transported to the gastrointestinal tract due to the natural process of chewing and salivation (Lai et al. 2018). Active compound delivery technologies adjust the drug release, absorption, distribution, and disposal profile for the benefit of improving product efficacy and safety, as well as patient convenience and compliance (Bae and Park 2020).

Methods of film production

Casting and extrusion techniques are the main and most used to prepare films for oral disintegration. However, in recent years, new techniques have emerged as some variants of casting and extrusion methods, such as tape casting and the printing technique.

Casting technique

The simplicity and low cost make the casting technique known as the solvent evaporation method the most used for the production of orally disintegrating films (Musazzi et al. 2020). In this technique, polymers, excipients and active compounds are dissolved in an aqueous solution, which can be subjected to stirring and heating for solubilization. The obtained solution goes through a drying process and then the formed film can be cut to the desired size (Niese and Quodbach 2019).

The production of films using the casting technique can be carried out in plates, such as Petri plates, controlling the average thickness of the film by the mass poured in suspension. Local variations are generally unavoidable and the process is not suitable for the formation of films larger than 25–30 cm, leading to difficulties in scaling up (De Moraes et al. 2013; Liu et al. 2017).

However, the casting technique, in general, still presents obstacles that limit large-scale production, due to the difficulty of producing films with larger dimensions and their long drying times (De Moraes et al. 2013; Musazzi et al. 2020). Several studies in the literature report the use of the casting technique for the production of orally disintegrating films (Borges and De Carvalho 2015; Ma et al. 2015; Singh et al. 2018a; Verma et al. 2018; Bodini et al. 2020).

Hot extrusion method

In the extrusion process, the raw materials must be able to deform easily inside the extruder, this due to the action of heat and solidify after leaving the extruder. Polymers, as well as other ingredients, are mixed in the dry state, subjected to a heating process and then extruded. In this process, solvents are eliminated (Suryawanshi et al. 2019).

The extrusion process is still little used for the production of orally disintegrating films, being little reported in

the literature, however, it presents some characteristics such as better uniformity of active compounds and reduced operational units (Suryawanshi et al. 2019). Reducing the number of steps allows the production process to be continuous, which makes this technique viable for large-scale film production (Suryawanshi et al. 2019). However, the major problem in using this method is the degradation of thermosensitive substances, due to the high temperatures used in the process (Dixit and Puthli 2009), which ends up limiting its use to some active compounds.

While having some advantages, a complete preformulation survey of various active compound delivery systems is necessary for the proper selection of an active compound, carrier and additives for the proper and continuous operation of the process to achieve the desired product (Tambe et al. 2021). The application of the extrusion technique to prepare orally disintegrating films is limited to a few examples as the polymers used to prepare the films, such as polysaccharides, are generally heat sensitive and/or exhibit a high glass transition temperature that cannot be easily adjusted with the addition of a plasticizer, which can result in very sticky or ductile films (Cilurzo et al. 2010; Karki et al. 2016).

Tape-casting

Tape-casting is a technique still little explored in the production of orally disintegrating films, but it has characteristics that can be interesting, in order to enable the production of FDOs on a large scale and in a short period of time. In this technique, the suspension is molded into a thin layer on the support, through the movement of a leveling blade (De Moraes et al. 2013). The filmogenic solution is spread on larger supports or even on continuous conveyor belts, which are subjected to drying by heat conduction, hot air circulation (heat convection) or infrared (De Moraes et al. 2013).

Vuddanda et al. (2017) produced FDOs loaded with tadalafil nanocrystals (TDF) by tape casting and investigated the effect of hydrophilic surfactants and drug loads on the physical–mechanical and dissolution properties. The authors comment that the mechanical properties of the films varied with changes in the drug and surfactant loaded. Significant changes were observed in the time of disintegration when compared to films produced without surfactants and the release of about 80% of the drug was observed between 3 and 30 min.

Printing technique

The printing technique has been studied in different works as an alternative to incorporate active compounds in orally disintegrating films (Buanz et al. 2015; Scarpa et al. 2017b; Vuddanda et al. 2017; Dodoo et al. 2020). In this method, it is necessary to obtain a polymer matrix without active principle, which can later be used as a substrate for printing a solution containing active compounds (Preis et al. 2015).

In this method, the compound is deposited on the substrate surface using a printer, allowing the active compound not to be degraded by mechanical and thermal stress caused during the film production and drying process. A drying temperature of these films can be higher, since the active ingredient will be incorporated at the end of the process (Borges et al. 2019).

This technique can be used to produce polymeric matrices with greater precision for incorporation of the active compound. Concentration can be designed by changing the printing solution or increasing the number of layers, in this way, the material can be produced on demand according to the need of each individual case (Buanz et al. 2015; Preis et al. 2015).

Borges et al. (2019) evaluated the effect of different extraction conditions and the incorporation of natural extracts from pomegranate (*Punica granatum* L.) as a source of active compounds in the production of oral films using the printing technique. The authors report that the highest active content was observed in the mesocarp (70 °C, 30 min and 70% EtOH), this extract had viscosity and contact angle that could potentially be used as a printing solution. The increase in printing layers led to an increase in phenolic compounds, with variation in microstructure and surface pH, showing that the printing technique can be used to incorporate these natural compounds in polymeric matrices to obtain oral films.

Applications of oral disintegration films in food products

Fast dissolving films have been gaining prominence in the area of food science and technology, as vehicles for transporting active ingredients, such as probiotics, vitamins, anthocyanins, curcumin, phenolic compounds, among others. Oral disintegration films have been considered the first choice for people with swallowing dysfunction, dysphagia, nausea, vomiting, or any other difficulty in administering other forms of injection of active ingredients (Slavkova and Breitkreutz 2015), or to improve absorption and still substituting for existing pharmaceutical forms. Some national pharmacies already produce orally disintegrating films, and the active ingredients available, as well as their quantity, depend on the consumer's need. Some application examples, depending on the active compound used, can be seen in Table 5.

Qin et al. (2019) produced films of chitosan and pullulan as vehicles for aspiration administration through electrospinning technology. The authors comment that the chitosan/pullulan ratio influenced the properties of

Table 5 Application of some orodispersable films

Type of films	Active principle	Film application	Reference
Mucoadhesive films	Fluconazole	Oral candidiasi	Rençber et al. (2019)
	Palonosetron	Antiemético	Nair et al. (2018)
	Omeprazole	Ulcer	Khan and Boateng (2018)
	Acyclovir	Herpes simplex	Al-Dhubiab et al. (2015)
Fast disintegration film	Levothyroxine	Hormone replacement	Zhang et al. (2015)
	Metformin hydrochloride	Antidiabetic	Haque and Sheela (2015)
	Omeprazole	Stomach problem	Khan and Boateng (2018)
	Aprepitanto	Antiemetic	Sharma et al. (2016)
	Zolmitriptan	Migraine	Prajapati et al. (2018)
	Buspirone hydrochloride	Anxiety	Bharti et al. (2019)

the solution and the morphology of the films, with the increase of chitosan, the viscosity and conductivity of the solutions increased. Besides, the films showed excellent thermal stability and solubility in water in 60 s.

The study of Heinemann et al. (2013) developed orally disintegrating (ODF) films for delivery of probiotics in the mouth. The ODF formulations were composed of *Lactobacillus acidophilus* or *Bifidobacterium animalis subsp. lactis* added in a matrix composed of carboxymethylcellulose, gelatin and starch. The viability of the microorganisms during the production of the films and during the storage was evaluated by the enumeration of viable cells, it was observed by confocal microscopy, and the counts showed less than 15% loss of probiotics during the process. The probiotics showed high viability during 90 days of storage, demonstrating that the product developed can be a simple and innovative vehicle for the regular ingestion of probiotics.

Cupone et al. (2020) developed an orodispersible film of maltodextrin for daily supplementation of Vitamin D3 (2000 IU) with the aim of improving adherence when compared to existing oral dosage forms. The stability evaluation showed that the vitamin D3 assay was $\geq 90\%$ after 3 months of storage at 40 °C. The film disintegrated in less than 1 min and the vitamin D3 released was $\geq 75\%$ after 15 min. It demonstrates that is suitable to be manufactured and used as an innovative form to consume vitamin D3 as food supplements.

In the study performed by Pereira et al. (2021), FDOs were produced based on a mixture of cassava starch and gelatin (1:1) with the incorporation of natural antioxidants, vitamin C and catuaba extract. The authors obtained films with good appearance and homogeneity, and all films produced with vitamin C and catuaba extract had their antioxidant capacity demonstrated, and the films of catuaba extract showed antioxidant capacity values between 6.65 and 57.56%, and the vitamin C films presented values between 75.62 and 100%. Also demonstrated that films loaded with vitamin C (10 g/100 g polymer) had the highest antioxidant capacity (93.33%) and are considered promising alternatives for vehicles for incorporating active compounds.

Garcia et al. (2020) produced orally disintegrating films (ODFs) based on pregelatinized starch and gelatin with the incorporation of acerola powder obtained from industrial waste. The authors evaluated the effect of the concentration of macromolecules on the properties of the films and its solubility. All films were soluble and through microstructure analysis by atomic force microscopy showed that higher starch concentrations led to greater heterogeneity and surface roughness. The inclusion of starch in the films increased the hydrophilicity of the material and it was also observed that higher levels of starch contributed to shorter disintegration times. The antioxidant capacity results showed that, after 50 days of storage (75% relative humidity and 40 °C), the ODFs retained at least 60% of their antioxidant capacity, representing a promising system for the delivery of active compounds.

Zhang et al. (2019) developed fast dissolving films with self-microemulsifying technology for vitamin D supplementation. The films showed good mechanical properties (thickness 166.7 ± 3.30 µm, tensile strength 38.45 ± 3.72 MPa, elongation $23.38 \pm 4.23\%$ and bending strength > 200 times), and its time of disintegration was about 18 ± 1.23 s.

Tedesco et al. (2021) produced and characterized oral films based on carboxymethyl cellulose (CMC), hydroxypropyl methyl cellulose (HPMC) and pregelatinized starch with the incorporation of ethanolic extract of dehydrated acerola industrial residue (EEDAIW) using the tape-casting technique. The authors report that the addition of EEDAIW to the films led to a reduction in the tensile strength of the films and an increase in the contact angle values, however, the surface pH of the films remained close to the oral pH (6.8).

Ockun et al. (2022) developed a fast dissolving film (FDO) containing anthocyanin-rich Vaccinium arctostaphylos L. fruit extract and evaluated the physical and phytochemical parameters of the formulation. The authors report that the incorporation of the extract promoted a reduction in tensile strength and Young's modulus, and an increase in the

elongation. Regarding the in vitro release, good results were obtained, the film showed maximum anthocyanin release (~98%) in 10 min.

Garcia et al. (2022) studied the development of agar-based oral films (OFs) with the incorporation of mushroom powder (MP) as a source of phenolic compounds. The surface pH of the films remained close to neutral (~6.7), regardless of the concentration of MP added. The incorporation of MP increased the crystallinity of the OFs compared to the agar-based film, however all the OFs presented similar FTIR spectra. Oral films containing 2 g of MP showed antioxidant capacity by ABTS + and FRAP of 3.68 ± 0.23 and 14.61 ± 0.66 mMol ET/g OF, and total phenolic content of 3.55 ± 0.27 µmol GAE/g OF, respectively. The data demonstrate that produced films offer an innovative source of delivery of active compounds as their consumption does not cause irritation to the oral mucosa.

Challenges and future perspectives

Despite appearing to be easy to produce, orally disintegrating films present extreme challenges in their manufacture and consumer acceptance. It is important to relate the film production technology to the active compounds of interest, as well as the broad consumer acceptance of the use of this innovative pharmaceutical form of active compound administration. It is important to emphasize that the characterization methodologies of these materials are not standardized, which leads to several methodologies available in the literature, making it difficult to compare important properties of films produced with different polymers.

Some important issues must be taken into consideration regarding the development and manufacture of oral films, as the quality attributes must be well established to avoid possible errors. Different techniques are available for the production of films, but they must be chosen according to the physicochemical properties of the active compound and its size. The use of different polymers of natural or synthetic origin can be made for the production of orally disintegrating films as carriers of active compounds.

The use of this new pharmaceutical form can reach different audiences, such as geriatric patients, children and animals, making the ingestion of active compounds and medications more practical, in addition to meeting specific needs such as dosage and quantity to be administered. Depending on the form of administration, orally disintegrating films are commercially available, but their use is still limited compared to other forms of administration such as tablets, pills, capsules, liquid forms, among others.

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Declarations

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