International Journal of Biological Macromolecules 178 (2021) 504–513

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: http://www.elsevier.com/locate/ijbiomac

Review

A review on orally disintegrating films (ODFs) made from natural polymers such as pullulan, maltodextrin, starch, and others

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ARTICLE INFO

Article history:
Received 21 October 2020
Received in revised form 19 February 2021
Accepted 23 February 2021
Available online 26 February 2021

Keywords:
Orodispersible film
Fast dissolving film
Oral strip
Casting
Disintegration time
Film-forming agent

ABSTRACT

In recent years, orally disintegrating films (ODFs) have been studied as alternative ways for drug administration. They can easily be applied into the mouth and quickly disintegrate, releasing the drug with no need of water ingestion and enabling absorption through the oral mucosa. The ODFs matrices are typically composed of hydrophilic polymers, in which the natural polymers are highlighted since they are polymers extracted from natural sources, non-toxic, biocompatible, biodegradable, and have favorable properties for this application. Besides that, natural polymers such as polysaccharides and proteins can be applied either alone or blended with other synthetic, semi-synthetic, or natural polymers to achieve better mechanical and mucoadhesive properties and fast disintegration. In this review, we analyzed ODFs developed using natural polymers or blends involving natural polymers, such as maltodextrin, pullulan, starch, gelatin, collagen, alginate, chitosan, pectin, and others, to overview the recent publications and discuss how natural polymers can influence ODFs properties.

Contents

1. Introduction

Oral dosage forms are the most common drug administration method due to the ease of administration, high patient convenience and compliance, minimum aseptic conditions, and flexibility in designing the dosage forms. However, there are several limitations for geriatric, pediatric, or dysphagic patients, people with difficulty in swallowing, and even animals [1]. As an alternative method to overcome these limitations, orally disintegrating systems were developed, aiming for a fast release of the drug without water ingestion, also enabling drug absorption directly through oral mucosa to enter systemic circulation, avoiding first-pass hepatic metabolism [2].

Orally disintegrating films (ODFs), also called orodispersible films, are thin polymeric films with the size of a postage stamp that quickly hydrate and adhere to the mucosa wetted by saliva, disintegrate their

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https://doi.org/10.1016/j.ijbiomac.2021.02.180
0141-8130/

matrices and release active compounds for absorption [3]. They must be thin, flexible, easy to handle and administrate, stable for manufacturing, packaging, and transportation processes. They also must provide acceptable taste and mouth-feel, with a short disintegration time (up to 1 min) [4]. The most common methods to produce ODFs include the solvent casting method [1,5] and hot-melt extrusion [5–7]. Still, electrospinning and printing technologies have also been studied as alternative ways to produce personalized ODFs [5].

The typical composition of an ODF consists of a drug or active compound, called active pharmaceutical ingredient (API); a film-forming polymer; a plasticizer agent to provide flexibility and enhance mechanical properties; fillers; saliva-stimulating agents to enhance salivation and facilitate disintegration; taste-masking agents such as flavors and sweeteners to cover the bitter and unpleasant taste of many APIs; coloring agents to make the film more attractive to consumers; and others, like surfactants, enzyme inhibitors, stabilizers, and thickening agents [4,8].

The film-forming polymer must be hydrophilic, non-toxic, non-irritant, and present spreadability and good mechanical properties [1]. The selection of the ideal polymer is still challenging once the polymer should be able to disintegrate as fast as possible in the oral cavity and, at the same time, provide mechanical resistance for handling, packaging, and storage [4]. Several polymers have been used in the literature, being synthetic and semi-synthetic, such as polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene oxide (PEO), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), polyethylene glycol (PEG), and poly (ε-caprolactone) (PCL); or natural polymers, such as pullulan, starch, maltodextrin, pectin, gelatin, alginate, and chitosan [1,6–8].

Attention has been paid to natural polymers compared to synthetic polymers, as they are macromolecules obtained from natural renewable sources (Fig. 1), which present favorable properties for several applications, including biomedical. Natural polymers are often naturally hydrophilic and non-toxic, present biocompatibility, biodegradability, and may have intrinsic mucoadhesiveness [9]. Besides, they can be combined with other synthetic or natural polymers to improve some characteristics, such as mechanical resistance and flexibility [10].

Therefore, in this manuscript, we reviewed the literature in which natural polymers were used alone or in combination with other polymers to develop ODFs, bringing a brief introduction to the main natural polymers used in ODFs, their properties, and main results. Since synthetic and semi-synthetic polymers have already been examined by other reviews on ODFs [2,11,12], as well as production and characterization methods [1–5,8], in this review, we focused on ODFs composition prepared with natural polymers, exploring the relationship between structure and properties.

2. Characteristics of natural polymer-based ODFs

The solvent casting method is the most used technique to produce ODFs [1]. Musazzi et al. [5] recently published a review about the main production methods of ODFs, including synthetic, semi-synthetic, and natural polymers, exploring the current trends and technologies for ODFs manufacturing.

Biopolymers-based ODFs are typically produced by casting technique [10] since they cannot easily be processed by other methods commonly applied to synthetic polymers, such as hot-melt extrusion. Studies using alternative methods such as electrospinning [13], freeze-drying [14], and heat drying methods [14] are also found in the literature for biopolymer-based ODFs, which may influence some characteristics, especially the film thickness.

Film thickness is an important parameter since ODFs should be thin enough to adhere to the mucosa without causing discomfort. At the same time, it should be thick enough to allow handling and manipulation. Uniformity in film thickness is also important since drug dose accuracy depends on film thickness. Moreover, the film thickness is taken into account for mechanical properties calculations, such as tensile strength. Typically, the thickness of ODFs is measured using a digital micrometer in at least five random positions along the film surface [8].

Besides, several properties should be investigated for the development of biopolymer-based ODFs, such as mechanical properties (tensile strength, elongation at break, Young's modulus, tear-resistance, and folding endurance), surface pH, contact angle, mucoadhesiveness, disintegration time (*in vitro*, *in vivo*), and dissolution of the active compound (Fig. 2). Characterization methods are not always standardized for these materials, so several methods are described in the literature with some variations, making it challenging to directly compare the properties of the films produced with different natural polymers [10]. For the most interested readers on the characterization methods of ODFs, we recommend reading Irfan et al. [8] and Lee et al. [1].

In general, *in vitro* disintegration time is evaluated by the slide frame method: a drop of water or simulated saliva is placed upon the film. The time until the film dissolves and forms a hole is considered the disintegration time. Another method to evaluate the *in vitro* disintegration time is the Petri dish method. The film is set in a Petri dish or a beaker with some water or simulated saliva. The disintegration time is evaluated as the time until the film completely dissolves. For ODFs formulations, the disintegration time typically varies from 5 to 30 s, depending on the film composition, especially the natural polymer [8].

Another essential parameter to be considered in the development of ODFs is the surface pH, which should be closed to the pH of the oral cavity, pH ≅ 6.8 [15,16]. Besides that, mechanical properties and mucoadhesiveness are also important parameters to be analyzed. There are no established standards for acceptable values of film mechanical properties and mucoadhesiveness. Still, the films must be strong and ductile to prevent rupture during the manufacture and packaging processes, flexible to provide a pleasant sensation in the oral cavity, and mucoadhesive to adhere to the mucosa allowing drug permeation. In the literature, it was found a variety of values, with tensile strength ranging from 0.04 to 50 MPa, elongation at break from 2% to more than 500%, folding endurance from 50 to more than 300 folds, and mucoadhesiveness from 0.4 to 1.9 N, depending on the film-forming polymer and production technique.

Film transparency is another property that is usually analyzed in ODF development. This property is not mandatory for ODFs characterization, but it is directly related to consumer acceptability [8].

ODFs research and commercial application increased highly in the last two decades. The first commercially available ODF was Listerine®,

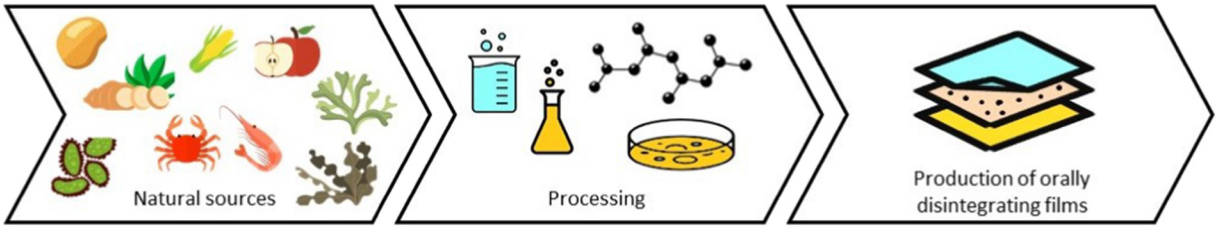

Fig. 1. Schematic representation of some sources of natural polymers, processing, and production of orally disintegrating films (ODFs). Figure developed by the authors using icons (designed by pch.vector, photoroyalty, and macro vector) obtained at Freepik.

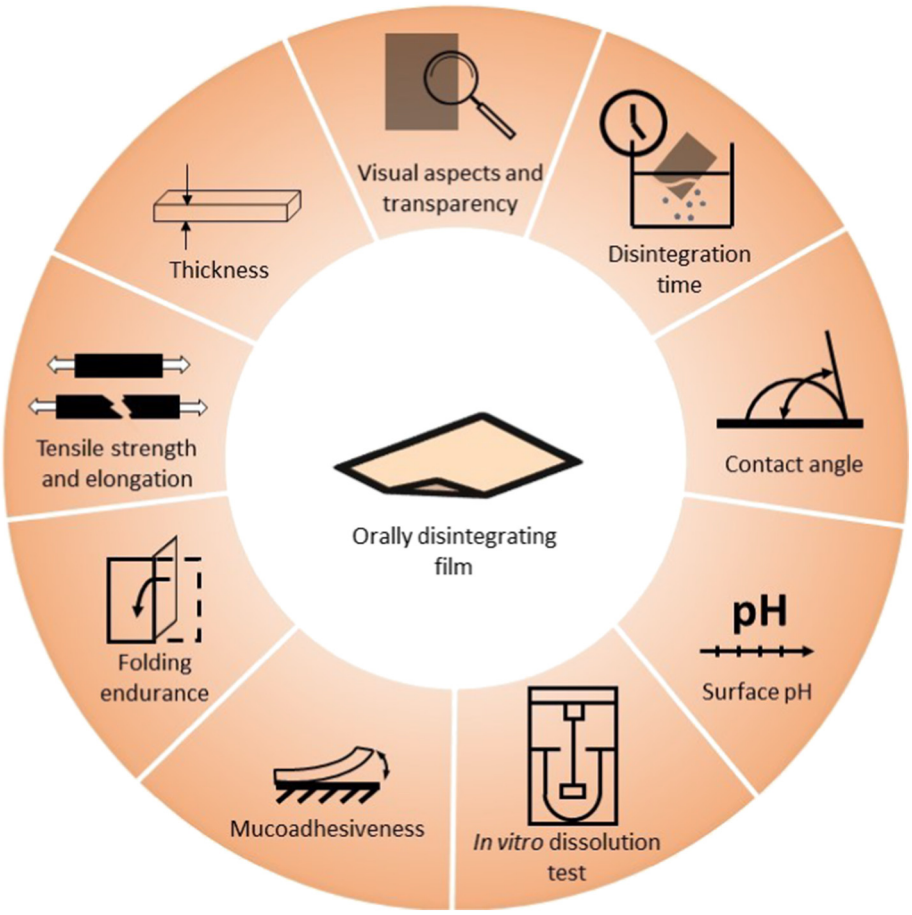

Fig. 2. Main characterization methods of orally disintegrating films (ODFs) made from natural polymers. Figure developed by the authors.

a mouth freshener launched by Pfizer in 2001. Since then, many commercial ODFs were introduced in the market, with uses varying from energy booster, to antiallergic and treatment of schizophrenia. The reviews published by Borges et al. [17], Lee et al. [1], Hoffmann et al. [4], and Dixit and Puthli [2] present a comprehensive overview of the commercially available ODFs and their main uses.

Considering the application and market potential of ODFs, the development of new formulations, the evaluation of the influence of various components, and the understanding of their properties are fundamental to the research advances in the area. To explore the use of natural polymers in the development of ODFs, we discussed the structure and the properties of main natural polymers and their influence in ODFs formulations, either used alone (Table 1) or blended with other synthetic or natural polymers (Table 2).

3. Natural polymers-based ODFs

The following sections present some natural polymers used as raw materials for ODF development.

3.1. Pullulan

Pullulan is an exopolysaccharide produced on the surface of microbial cells. It is produced mainly by yeasts such as fungus *Aureobasidium pullulans* and other microorganisms like *Cytaria darwinii*, *Cytaria harioti*, *Teloschistes flavicans*, *Tremella mesenterica*, *Rhodotorula bacarum*, and *Cryphonectria parasitic* [43,44]. In pullulan production, the main requirements are carbon source, nitrogen source, and other essential nutrients for *A. pullulans*' growth. Pullulan is a linear glucan with repeating units of maltotriose. Each maltotriose unit constitutes two α-(1 → 4) bonded glucopyranose rings interlinked by α-(1 → 6) linkage. When partial acid hydrolysis happens, there are rare forms of pullulan constituting panose and isopanose as repetitive units [45].

Pullulan is a non-ionic, non-hygroscopic, non-toxic, non-mutagenic, and non-carcinogenic biopolymer. The viscosity of the solution usually is lower compared to other biopolymers. Besides, pullulan is biodegradable, edible, odorless, tasteless, and shows solubility in hot and cold water and dilute alkali [43,45]. Due to its characteristics, pullulan has been extensively used for food, pharmaceutical, and biomedical applications. The food industry uses it as a stabilizer, binder, intensifier, beverage filler, dietary fiber, thickener, texture improver, and food packaging. Concerning the pharmaceutical and biomedical applications, it is employed as adhesives and denture pastes, capsule coatings, drug delivery, gene delivery systems, vaccination, tissue engineering [43,45], hydrophilic coatings for scaffolds [46], among others.

For the production of ODFs, pullulan is used due to its good film-forming properties; however, pullulan has a high cost, so it is usually blended with synthetic, semi-synthetic, and natural polymers to decrease cost and improve other properties. Literature shows pullulan ODFs blended with HPMC [37,47,48], pectin [47,49], maltodextrin [50], polyvinylpyrrolidone (PVP) [51], trehalose [52] and okra biopolymer [48]. Also, fillers such as cellulose nanofibers (CNF) were proposed to improve the compatibility, and tensile strength of pullulan/HPMC blended ODFs [37].

In addition to the blends and compatibilizers, plasticizers are added to overcome pullulan films' brittleness [49,53]. Vuddanda et al. [53] studied the effect of plasticizers with various physicochemical properties, such as glycerol, vitamin E TPGS, and triacetin in pullulan ODFs, concluding that glycerol in a concentration of 20–30% (*w*/w) is an excellent plasticizer to achieve acceptable physicochemical properties of

Table 1
Natural polymers used in the production of ODFs and the films' main properties.

Natural polymer	Natural polymer concentration	Active compound	Thickness (mm)	TS (MPa)	EB (%)	Surface pH	Disintegration time (s)	Ref
Maltodrextin (DE 6)	9% (w/w)	Benzidamine hydrochloride	168.4 ± 10.1	8.866 ± 0.302	8.75 ± 1.25	5.4 ± 0.1	17.6 ± 2.9	[18]
Maltodextrin	9% (w/v)	Sumatriptan succinate	0.295 ± 0.01		70.25 ± 0.7	6.85 ± 0.07	32	[19]
Maltodextrin	68.4% (w/w) (related to the total film weight)	Diclofenac sodium	119 ± 6	1.805 ± 0.060	30.57 ± 3.04		13 ± 1	[20]
Pullulan	2%–6% (w/v)	Ebastine	0.07–0.12	0.0902–0.0915	75.33–90.02	6.53–6.83	17.62–19.56	[21]
Pre-gelatinized starch	2% (w/w)		0.058 ± 0.002	20.8 ± 1.4	2.5 ± 0.2		43.7 ± 2.0	[22]
Pre-gelatinized starch	2% (w/w)		0.070 ± 0.004	29.7 ± 3.1	3.6 ± 1.2	6.87 ± 0.002	10	[15]
Pre-gelatinized starch	2% (w/w)	Camu-camu powder	0.069–0.072	33.7 ± 3.8	2.1 ± 0.8	4.9 ± 0.1	10.3 ± 0.8	[23]
Pre-gelatinized starch	2% (w/w)	Acerola powder	0.071 ± 0.006			6.1 ± 0.2	~9	[24]
Modified rice starch	~43.8% (w/w) (related to the total film weight)		0.1144 ± 0.0018	0.480 ± 0.035	543.8 ± 80.9	4.54 ± 0.01	61.2–66.6	[25]
Gelatin	2% (w/w)	Propolis ethanolic extract		31.3 ± 2.9	48.2 ± 4.3		~540	[26]
Gelatin	2% (w/w)		0.070 ± 0.003	73.0 ± 3.4	14.0 ± 5.9	6.87 ± 0.009	<35	[15]
Gelatin	2% (w/w)	Camu-camu powder	0.069–0.072	11.9 ± 2.6	11.0 ± 6.8	5.7 ± 0.3	20.4 ± 0.8	[23]
Gelatin	2% (w/w)	Acerola powder	0.069 ± 0.005			5.8 ± 0.4	~20	[24]
Gelatin	2% (w/w)			51.52 ± 4.07	2.82 ± 0.22	6.21–6.73	34.43	[27]
Sodium alginate	1.25% (w/v)	Piroxicam	0.104 ± 0.005	3.13 ± 0.27	3.31 ± 0.32		20.33 ± 2.66	[28]
Chitosan	0.26%–0.3% (w/v)	Donepezil	0.24–0.38	48.05–69.63		6.7–7.2	20–41	[29]
Chitosan	8.33% (w/v)	Piroxicam	0.36–0.46	0.045–0.056	15.75–31.33	6.64–6.88	22.36–36.66	[30]
Chitosan	1.5%–3.0% (w/w)	Chitosan	0.162–0.183	~8.0	~2.0		5.43–14.43	[31]
Pectin	3.3%–4.3% (w/v)	Ezitimibe	0.124–0.265			6.75–6.80	26–60	[32]
Pectin	3% (w/v)	Coumarin	0.097–1.090			5.1–7.1	36–40	[33]

pullulan films for ODF application. On the contrary, Sharma et al. [49] compared the plasticizing effect of sorbitol, glycerol, and liquid glucose in pullulan/tamarind pectin films, concluding that liquid glucose exhibits the highest folding endurance, enhancing flexibility, and lower disintegration time. It is impossible to compare both studies since they evaluate different plasticizers; however, we can infer that liquid glucose and glycerin are good plasticizer options to be investigated in pullulan-based ODFs.

Also, flavor maskers are used, considering that most of the drugs have a bitter taste and aim to better patients' compliance, such as aspartame [21], sucralose, and monoammonium glycerinate [54]. The addition of tamarind pectin in ODFs with pullulan, besides decreasing disintegration and wetting time and increasing folding endurance, also masked the bitter taste of the aprepitant drug, becoming an antiemesis option during cancer chemotherapy. Takeuchi et al. [55] aimed to develop an electronic taste sensor system to evaluate the bitterness of ODFs using a pullulan film loaded with donepezil hydrochloride as a model. The results were satisfactory, and this system could be an excellent alternative to *in vivo* tests with human volunteers.

Some studies on pullulan ODFs also analyzed the influence of the drug in the film's properties, using isoniazid [47], influenza vaccine (H5N1) [39], citalopram [48], dihydroergotamine mesylate [50], ebastine [21], captopril [37], potassium diclofenac [54], donepezil hydrochloride [56], tetrabenazine [57,58], levocetirizine dihydrochloride [59], griseofulvin [60], aprepitant [49] and sodium diclofenac [51]. Pullulan-based ODFs have also been used as class II drug carrier, which has high permeability and low solubility. The films were prepared using xanthan gum as a thickening agent and glycerol as a plasticizer and exhibited excellent drug content uniformity, high tensile strength, and low elongation at break. The results indicate that pullulan is a good matrix for the fast release of poorly water-soluble drugs, improving its bioavailability [60].

The solvent casting process is the most used for pullulan ODFs production, but some attempts have been made with other manufacturing methods. Tian et al. [52] studied air- and freeze-drying methods to produce pullulan/trehalose ODFs loaded with proteins. Freeze-dried ODFs had a slightly shorter disintegration time than air-dried ODFs, probably due to the porous structure, with values ranging from 18 to 30 s, depending on the trehalose/pullulan weight ratio. On the contrary, the tensile strength and Young's modulus of air-dried ODFs were significantly higher than that of freeze-dried, which were very brittle, suggesting that air-drying solvent casting method is still the most adequate. Another exciting alternative to casting is the electrospinning method. The electrospinning method produces amorphous fibrous films with greater flexibility and plasticity. This method was recently used to develop pullulan-based ODFs for isoniazid delivery. The spinning solutions

Table 2
Blends containing natural polymers used in the production of ODFs and the films' main properties.

Natural polymer	Blend proportion	Active compound	Thickness (mm)	TS (MPa)	EB (%)	Surface pH	Disintegration time (s)	Ref
Maltodextrin + HPMC	5:7	Benazepril	0.083 ± 0.006			6.93 ± 0.11	10 ± 3	[34]
Maltodextrin + HPMC	3:7	Mosapride	0.21 ± 0.06	12.2	23.3		1	[35]
HPMC + maltodextrin	8:1	Montelukast sodium	0.20 ± 0.02	0.263 ± 0.006		6.91 ± 0.021	9.7 ± 1.12 s	[36]
Pullulan + HPMC	1:3	Captopril	68.0 ± 0.5	18.5	16.0		13.0	[37]
Trehalose + pullulan	4:6	Proteins	0.18	25	13		31	[38]
Trehalose + pullulan	4:1	H5N1 - influenza virus vaccine	0.119 ± 0.006	2.37 ± 1.03	6.24 ± 1.58		22.67 ± 1.24	[39]
Pre-gelatinized starch + HPMC	4:1	C. verbenacea extract	0.061–0.067	2.3–10.8	2.8–9.1		22.1–32.8	[40]
Wheat starch + HPMC + PEG	3:1:3		0.586 (HD) 0.635 (FD)	0.067 (HD) 0.044 (FD)			183.5 (HD) 165.7 (FD)	[14]
Gelatin + HC	7:3	Propolis ethanolic extract	0.067–0.070	18.5–25.9	41.1–45.9		~360	[26,41]
Gelatin + HC (with lecithin)	8:2		0.066 ± 0.003	13.5 ± 1.9	65.5 ± 6.6		21.3	[42]
Gelatin + HPMC	1:1	Peanut skin extract	0.050 ± 0.005	20.49 ± 1.31	3.27 ± 0.26	6.36–6.88	25.94 ± 2.99	[16]

were prepared using pullulan with HPMC, pectin, or sodium caseinate. All formulations disintegrated in 15 s, with total drug release in 60 s, presenting properties suitable for application as ODFs [47].

Therefore, pullulan is a promising natural polymer for application in ODFs formulations as a film-forming agent alone or blended with other polymers, such as maltodextrin and HPMC. It has been studied as a vehicle for several active compounds, presenting good film properties for oral administration.

3.2. Maltodextrin

Maltodextrin is a non-sweet nutritious oligosaccharide, used as a food additive, being easily digestible and absorbed. It is produced by hydrolysis from starch and is found commercially as a white hygroscopic powder. Three to nineteen units of D-glucose constitute maltodextrin. The bonds between the glucose units are mainly linked to the glycosidic bond α-(1 → 4). Maltodextrin is classified according to the dextrose equivalent (DE), ranging from 3 to 20. The smaller the glucose chain, the higher the DE and, consequently, more soluble . Maltodextrin has the following properties: good film former, odorless, good solubility, low hygroscopicity, excellent carrier, non-toxic, edible, soluble in water, and poorly soluble or even insoluble in anhydrous alcohol [11,61].

Maltodextrins can be produced with different raw materials, hydrolysis methods, and process conditions, resulting in various maltodextrins with unique physical and chemical properties for several applications [11,61]. Although maltodextrin is widely used in the food industry, it has also been studied in biomedical and pharmaceutical applications as a film-forming agent for ODFs, showing good mechanical properties and fast disintegration.

The dextrose equivalent (DE) seems to play an essential role in defining the properties of maltodextrin ODFs. Lower DE resulted in ODFs with higher tensile strength and lower elongation, lower moisture content, and shorter disintegration time (in the range of 15–30 s) [18]. The same trend of the stiffer and less ductile film in low DE was observed by Cilurzo et al. [62]. However, all the formulations exhibit the same disintegration time (approximately 10 s), regardless of the maltodextrin DE. Thus, special attention should be paid to the DE in the development of maltodextrin ODFs.

Maltodextrin has been explored in ODFs due to its good film-forming properties. It can be used alone or blended with HPMC [34–36,63,64], the most used semi-synthetic polymer to develop ODFs. Some studies also report blending of maltodextrin with pullulan [50], dextran [65], karaya gum, and xanthan gum [66].

Another interesting approach is to load ODFs with fillers. Franceschini et al. [67] increased the tensile strength in 1.5 times and the elastic modulus in four times by adding polyvinyl acetate (PVAc) nanofiller at maltodextrin-based ODFs at concentrations of 3 and 5% w/w of PVAc. Musazzi et al. [68] developed maltodextrin ODFs containing melatonin-loaded solid lipid microparticles without significantly altering the microparticles and the films' mechanical properties. Besides, the films containing more maltodextrin presented the highest tensile strength and faster release profile of the melatonin in the simulated salivary fluid. Maltodextrin was also used as a film-forming agent of ODFs for quercetin nanocrystals delivery. When quercetin was added, the films showed higher elongation at break, probably related to the low interfacial interaction between quercetin nanocrystals and maltodextrin matrix and fast dissolution profile [69].

Also, plasticizers are added to improve the mechanical properties of maltodextrin-based ODFs. The following plasticizers are normally used to enhance the ductility of maltodextrin ODFs: glycerin [65,69,70], sorbitol [18,63,65], xylitol [18] and propylene glycol [63,70]. Besides, non-traditional plasticizers such as amino acids glycine and proline were evaluated to maltodextrin ODFs, showing good potential to improve the film's ductility [71]. Plasticizers such as PEG 400 and esters of citric acid are not recommended since they have low miscibility with maltodextrin [70]. Maltodextrin ODFs plasticized with propylene glycol exhibit higher elongation at break and lower tensile strength than the same films plasticized with glycerin [70]. However, although both films presented quick disintegration time, films with propylene glycol were discarded due to volunteers' unpleasant taste during *in vivo* tests, compromising patients' compliance.

The most used method to produce maltodextrin-based ODFs is solvent casting; however, other manufacturing techniques have also been explored. Cilurzo et al. [70] compared the casting method with hot-melt extrusion to develop maltodextrin ODFs loaded with piroxicam. They concluded that the casting method is more indicated, exhibiting the highest patients' compliance, better *in vitro* and *in vivo* disintegration time, improving the dissolution of poorly soluble drugs as piroxicam. In an attempt to produce personalized ODFs, in which dimensions and drug dose would be adjusted to each patient, 3D printing was proposed by Elbl et al. [72] and Musazzi et al. [73], resulting in films with high flexibility and low disintegration time. These results indicate the potential use of printing technologies to develop on-demand and personalized ODFs.

Therefore, maltodextrin films generally exhibit high flexibility and rapid disintegration due to their hydrophilic nature, making maltodextrin a promising natural polymer for application in ODF formulations as a film-forming agent alone or blended with other polymers such as HPMC.

3.3. Starch

Starch, an abundant polysaccharide, presents two macromolecules: amylose and amylopectin. Amylose is a linear polymer of α-1,4 anhydroglucose units that forms a colloidal dispersion in hot water and has excellent film-forming ability. Amylopectin is a highly branched polymer of α-1,4 anhydroglucose chains linked by α-1,6 glucosidic branching points, being completely insoluble [10,74]. Starch can be obtained from various sources such as botanical species like corn, wheat, potato, cassava, and rice, and the starch of each origin has specific compositions and different properties [10]. The semi-crystalline nature of native starch can present undesirable characteristics, such as low solubility or poor mechanical properties. It may be chemically, enzymatically, or physically modified to enhance its properties and functionality [75,76].

Starch and modified starches are extensively applied in the food industry [74]. They have been studied for pharmaceutical and biomedical applications, such as excipients, substrates for cell seeding, scaffolds for tissue engineering, drug delivery systems, and bone replacement implants [76]. Besides, starch materials present the ability to form transparent, odorless, tasteless, and biodegradable films [23], which are favorable properties for ODF applications. Several authors have applied starch in ODF formulations as components of the matrix. They are involved as leading film-forming agents [15,23–25,77], blended with other biopolymers [15,23,24,78,79], or blended with synthetic or semi-synthetic polymers [14,22,78,79].

The properties of ODFs made from starch may depend on the starch source and mainly on the starch modification before use. The use of pregelatinized cassava starch seems to be a good option in the development of ODFs, with low disintegration time (in the order of 10 s) and high tensile strength (in the order of 30 MPa) [15,23,24]. Changing the starch source from cassava to corn increased the disintegration time to 40 s, as observed by Guerra et al. [77] in the development of ODFs from pre-gelatinized corn starch. The use of ball-milling as a physical modification of rice starch was also proposed as an alternative, resulting in a disintegration time of 1.11 min and tensile strength in the order of 0.5 MPa [25].

Blending starch with other polymers is also an attractive approach for the development of ODFs with suitable properties. When combined with gelatin, the increase in the starch content resulted in an increase in hydrophilicity [15], tensile strength, and a decrease in the disintegration

time [15,23], while mucoadhesiveness was kept constant [24]. On the other hand, when blended with HPMC, the starch content increase led to increased disintegration time and mucoadhesiveness [22].

Various methods to produce starch-based ODFs may also be used as alternatives to the traditional casting method. Liew et al. [14] investigated the use of wheat starch blended with HPMC and PEG for the development of ODFs by freeze-drying (FD) and heat drying (HD) methods. The increase in HPMC and starch concentrations increased tensile strength and disintegration time, being the Starch:HPMC:PEG (3:1:3) blend the optimized proportion of the components. Besides that, freeze-dried films showed lower tensile strength but better folding endurance and disintegration time than heat-dried films, indicating the influence of the production method on the film properties.

Starches are usually promising biopolymers for ODFs as film-forming agents; however, modified or pre-gelatinized starches are even more suitable for this application. They can form homogeneous and hydrophilic films, besides presenting good mechanical properties, fast disintegration, and high mucoadhesiveness.

3.4. Hydrolyzed collagen and gelatin

Collagen is an animal protein from the extracellular matrix of mammalian connective tissues. Collagen maintains the extracellular matrix's biological and structural integrity, providing mechanical strength, stimulating cell adhesion and proliferation, and being a dynamic and flexible material to refine cellular behavior and tissue function [10,80]. There are several types of collagen, but type I is the most commonly used. Collagen molecules comprise three polypeptide chains that form a triple-helical structure stabilized by hydrogen bonds with ~300 kDa molar mass, mainly formed by the amino acids glycine, proline, and hydroxyproline [80,81].

Denaturation of native collagen followed by hydrolysis by proteolytic enzymes results in hydrolyzed collagen (HC), composed of small peptides with low molar mass. HC presents low viscosity solution, antioxidant capacity, antimicrobial activity, bioavailability, and high solubility. It is employed in the cosmetic, pharmaceutical, biomaterials, food, and nutraceutical industries. However, due to its low molar mass, HC is not suitable for film production or scaffolds by itself, so it is usually applied combined with other biopolymers [81].

Gelatin is a protein derived from the thermal denaturation and acid or alkaline partial hydrolysis of collagen. Its structure consists of a polypeptide mixture of α-, β-, and γ-chains, with a typical amino acid composition of Ala-Gly-Pro-Arg-Gy-Glu-4Hyp-Gly-Pro-. When gelatin is obtained by acid treatment of collagen, it is classified as type A, while when obtained by alkali treatment of collagen, it is classified as type B. The most used sources of extraction are bovine, pigskin, bones, and fish skin. Gelatin is water-soluble, and its properties depend on the characteristics of the initial collagen and the extraction process. It presents film-forming capacity, gel formation, adhesion, cohesion, transparency, thickening, and water-binding capacity. It is widely used in the food industry as a gelifier, stabilizer, emulsifier, and texture agent for several products [82]. In health applications, gelatin is employed in wound dressings, drug delivery, and oral films, exhibiting properties like biodegradability, biocompatibility, non-immunogenicity, mucoadhesiveness, and film-forming ability [10,23].

The addition of HC to gelatin-based ODFs increases the films' flexibility and makes the films more hydrophilic, with low values of contact angle and fast disintegration. This behavior may be related to the low molecular weight of HC molecules compared to gelatin [26,41,42].

Gelatin-based ODFs presented high tensile strength and mucoadhesiveness compared to other natural polymers [15,23,24,26,41,42,79]. However, the films seem to have poor hydrophilicity when gelatin was used alone. It was blended with HC [26,41,42], starch [15,23,24,79], CMC [79], and HPMC [27], in which the increase in the proportion of the other blend components increased hydrophilicity and reduced disintegration time of the ODFs. When blended with starch [24] or HC [26], the films kept the mucoadhesiveness constant regardless of the blends' proportion, but with HPMC [27], the increase of gelatin proportion increased the blends' mucoadhesiveness.

The method used to evaluate the disintegration time also affect gelatin-based ODFs. Several studies used the slide frame method, in which the disintegration time is the time needed for a drop of solution placed on the top of the film to dissolve the film, forming a hole. These studies presented suitable disintegration times, in the order of 30 s [15,23,24,27,42]. On the other hand, when the Petri dish method was used, the sample is immersed in a solution and considered the time needed to disintegrate the film completely. The studies presented disintegration results over 5 min [26,79]. However, when Kwak et al. [83] used fish gelatin compared to the pigskin type A gelatin commonly used in other studies to produce ODFs with caffeine, they obtained a disintegration time of 40 s by the Petri dish method. This indicates that the gelatin source could also play an important role in the ODF final properties.

In general, there are few studies using collagen in the development of ODFs, but it seems that HC enhances hydrophilicity and disintegration properties when blended with other biopolymers. Besides that, gelatin shows good potential for application as ODF, primarily when used in combination with other polymers, in which gelatin acts as an enhancer of mechanical strength and mucoadhesive properties.

3.5. Alginate

Alginates are salts of alginic acid, a natural anionic polysaccharide found mostly in brown algae species, such as *Macrocystis pyrifera* and *Laminaria hyperborea* [84]. Alginates are copolymers which structure consists of (1 → 4) glycosidically linked β-D-mannuronic acid (M) and α-L-glucuronic acid (G) monomers in either similar or alternating covalent sequences or blocks (MMMM, GGGG, or GMGM). The proportion and distribution of these blocks depend on the alginate source and determine the biopolymer's properties. According to its properties, they can be used as films [85], membranes [86,87], hydrogels [88], microparticles [89], capsules for cells in the treatment of diabetes, among others [90–93].

Alginate in solution is an anionic polyelectrolyte; moreover, it presents biocompatibility, low toxicity, immunogenicity, stability in physiological conditions, and ability to form gels in the presence of divalent cations, *e.g.*, Ca^{2+} and Mg^{2+}. Films of sodium alginate present high hydrophilic characteristics, with low mechanical properties and water resistance, usually crosslinked with Ca^{2+} to enhance mechanical and water resistances. Alginate has been extensively studied and used for food, biomedical, and pharmaceutical applications due to its swelling and gelation abilities, creating a moist environment favorable for use in wound dressings formulations [90,91]. It has also been applied in ODFs formulations as a film-forming agent or combined with other polymers [10].

Alginate-based ODFs presented high tensile strength and high hydrophilicity with disintegration time within 60 s [28,63,94]. Murthy et al. [94] tested three different alginate concentrations, and the highest one resulted in the film with the fastest disintegration (22 s). However, El-Bary et al. [28] compared HPMC-based films and concluded that HPMC-based ODFs presented similar disintegration times with higher mechanical strength.

When blended with HPMC, tensile strength and disintegration time varied according to the blend proportion. The proportion of 4:1 (Alginate:HPMC) resulted in ODFs with reduced tensile strength and slower disintegration than the alginate film in the same study [63]. On the other hand, the proportion of 1:2 (Alginate:HPMC) resulted in ODFs with higher tensile strength and faster disintegration than alginate alone in the same study [95]. Alginate was also blended with xanthan gum, with HPMC and maltodextrin [63], and with PVA and PEG400, in which the ODFs presented high flexibility and a fast disintegration within 20 s [96].

Thus, alginate films represent good systems to ODFs formulations, promoting hydrophilic characteristics and suitable disintegration time. It has also been studied in blends with other polymers to improve its mechanical properties. However, few studies have explored alginate as a film-forming agent in ODFs, indicating that there is still much to be explored, such as blends with other natural polymers, as well as its mucoadhesive potential.

3.6. Chitosan

Chitosan is produced by partial deacetylation of chitin, a natural polysaccharide found in exoskeletons of arthropods such as insects and crustaceans, and fungi cell walls. Chitin is made up of *N*-acetylglucosamine units, while chitosan is a cationic polymer consisting of a linear sequence of monomeric units of 2-acetamido-2-deoxy-D-glucopyranose 2-amino-2-deoxy-D-glucopyranose linked by β(1 → 4) glycosidic bonds. Chitin is insoluble in common solvents due to its highly crystalline structure. On the contrary, chitosan can be easily dissolved in aqueous acidic solutions, making it suitable for various applications [97,98].

Chitosan can be molded in different forms like gels [99], beads [100], membranes [86,101], sponges [102], films [103], tubes [104], and fibers [105]. Chitosan devices present biodegradability, biocompatibility, low toxicity, and antimicrobial activity. Several applications have been reported with chitosan like food packaging, biomaterials for tissue engineering, drug delivery systems, edible films, and coatings, among others [106,107]. Besides, chitosan presents mucoadhesiveness, which is an essential property for oral film formulations [9,13,108]. However, few studies applying chitosan into ODF formulations were found in the literature.

Chitosan molar mass, particle size, and concentration in solution seem essential in developing suitable ODFs. The films produced using low molecular weight chitosan presented better physical-chemical properties and better sensorial analysis results than medium molecular weight chitosan. All films presented fast disintegration, but when chitosan concentration increased, disintegration time alsoincreased [31]. Also, nano-sized chitosan-based films showed faster disintegration compared to micro-sized ones [29]. When sodium starch glycolate and crospovidone were used as super disintegrating agents, chitosan-based ODFs also had a fast disintegration, below 36 s [30].

Several plasticizers were used in the development of chitosan-based ODFs, such as glycerol [29,31], sorbitol [31], PEG400 [30], and PEG600 [29]. In general, the chitosan films presented high tensile strength and flexibility. When super disintegrating agents were used, the films exhibited lower tensile strength. In addition, the films' properties were similar to CMC-based films developed in the same study [30]. Besides that, chitosan was also used as a mucoadhesive agent to HPMC-based films to enhance drug permeability [109].

The use of chitosan in ODFs formulations is still little explored, being more used due to its mucoadhesive property. Also, the concentration of chitosan solution used to prepare the films and the molar mass, particle size, and the addition of super disintegrating agents and other excipients play a significant role in developing suitable ODFs, with short disintegration time and good mechanical properties.

3.7. Pectin

Pectin is a complex mixture of polysaccharides found in cell walls, where its function consists of contributing to tissue integrity, rigidity, and hydration [10,110]. Poly α1–4-galacturonic acids compose pectin with varying degrees of methylation of carboxylic acid and amidated polygalacturonic acids. According to the ratio of esterified galacturonic acid groups, it can be classified as high methoxyl pectin (HMP) and low methoxyl pectin (LMP). HMP can form a gel in acidic media in the presence of sugars like sucrose or glucose, while LMP forms a gel in the presence of multivalent ions that binds pairs of carboxyl groups of different pectin chains [110].

Pectin is a water-soluble biopolymer extensively used in the food industry as a gelling, stabilizing, and thickening agent in jams, yogurts, fruity milk drinks, and ice creams, and it has been studied for applications as packaging and edible films [110]. Pectin has also been applied in the research and development of natural medicines and health products due to its wide availability. It can be used for drug delivery systems as gel beads, films, and matrix tablets [111].

Just a few papers used pectin in ODF formulations as a film-forming agent, making it difficult to compare studies and understand the real influence on films' properties. Reddy and Murthy [32] used several concentrations of commercial pectin as the film-forming agent to develop ODFs. The increase in the pectin concentration increased the films' thickness and flexibility, increasing the disintegration time, indicating that the use of a lower concentration is more suitable for developing a pectin-based ODF. When blended with pullulan, pectin extracted from tamarind enhanced the properties of the ODFs produced. It was used a low concentration of tamarind pectin, in which the increase in the proportion of the pectin in the blend decreased the disintegration time [49].

Thus, pectin is a promising film forming agent for ODF formulations. It is hydrophilic and provides flexibility and fast disintegration. However, the films' final properties may depend on the pectin's source and the concentration of the filmogenic solution. Therefore, pectin from various sources either alone or blended with other polymers can still be more explored for the application as ODFs.

3.8. Other biopolymers

Other biopolymers have also been explored for application into ODFs formulations, such as xanthan gum, karaya gum, moringa gum, okra, and hyaluronic acid.

Xanthan gum is a natural polysaccharide produced by bacteria of the genus *Xanthomonas*, composed of D-glucosyl, D-mannosyl and D-glucuronyl acid residues with varying proportions of *O*-acetyl and pyruvil residues [112,113]. Xanthan gum has been used in biomedical applications such as wound dressings due to its excellent biocompatibility and gelling property [10,112]. Sheikh et al. [114] used xanthan gum as a film-forming agent in ODFs and obtained films with better physicochemical and mechanical properties than HPMC, HEC, and PVA films. The films disintegrated between 17 and 27 s and released the drug faster than other formulations, indicating the potential use of xanthan gum for ODFs application. On the other hand, Sayed et al. [115] obtained xanthan gum films with longer disintegration time and lower tensile strength than HPMC, alginate, and maltodextrin films. When maltodextrin was blended with xanthan gum to deliver rizatriptan benzoate, the films presented good folding endurance and better drug release than maltodextrin-based films [66]. Xanthan gum was also added to HPMC ODFs as a film-modifier and resulted in films with improved physicochemical properties [116]. Other studies used xanthan gum and other gums, such as Arabic gum, as thickening agents to develop ODFs formulations [60,117].

Vidyadhara et al. [66] used karaya gum, an exudate gum polysaccharide extracted from *Sterculia urens* trees [118], in combination with maltodextrin to develop ODFs. The formulations with karaya gum presented lower folding endurance values but showed an average drug release of 79–90% within 15 min, which was enhanced compared to maltodextrin alone.

Shahzad et al. [48] developed ODFs based on HPMC with okra biopolymer, a natural polysaccharide extracted from the okra plant (*Abelmoschus esculentus L.*), and moringa gum, a natural gum obtained from the *Moringa oleifera* plant. All formulations showed neutral surface pH and disintegration time in a range of 11–25 s. Based on mechanical properties such as tensile strength and elongation, the authors concluded that the films containing okra biopolymers were more adequate for application as ODFs.

Recently, Kim et al. [119] showed the potential of applying hyaluronic acid (HA) as ODF. The films' physical properties depend on the molecular weight of HA: low molecular weight HA seems to be

more suitable for application as ODFs with fast disintegration and good mechanical properties. Other studies also applied modified HA as a mucoadhesive excipient for drug delivery systems [120,121].

Thus, several biopolymers as gums have been used as film-forming agents, thickening, or film-modifiers in ODF formulations to improve film properties, providing good hydrophilicity, viscosity, flexibility, and swelling capacity.

4. Future trends

Orally disintegrating films represent advantageous drug administration methods to the elderly, pediatric, and dysphagic patients and may even be a new method of vaccine dosage forms. Several natural polymers present suitable properties for application into ODFs formulations. However, the natural polymer selection still represents a challenge since it plays a significant role in the films' final properties. Besides, it is difficult to simultaneously achieve adequate mechanical resistance, flexibility, mucoadhesiveness and disintegration time. That is why ODFs are generally developed by blending natural polymers with other synthetic or natural polymers to combine their properties and achieve better results.

Despite the advances in the area in recent years, there is still a lot to be explored in the development of ODFs. Some natural polymers commonly studied for biomedical and pharmaceutical applications as drug delivery systems could also be explored for application as ODFs, such as guar gum, gellan gum, carrageenan, and other exudate gums, among other natural polymers. Many of them present desirable properties such as hydrophilicity, film-forming capacity, and mucoadhesiveness. Recently, attention has been paid to the use of lignin as an excipient for pharmaceutical products, like tablets and drug-controlled release devices [122–124]. Pishnamazi et al. [123,124] showed that lignin-based tablets have faster disintegration than non-lignin tablets, indicating its potential to be explored into ODFs formulations. Silk fibroin, a protein present in silk produced by silkworms, has also been widely studied for pharmaceutical applications and in drug delivery systems formulations [10], but still little explored in ODFs. However, silk fibroin has good mucoadhesive properties [9,125]. Besides, blending different natural polymers may enhance several properties and promote adequate characteristics to develop new ODF matrices.

Many techniques have been applied for ODFs development. Although solvent casting is the most used, new technologies such as inkjet, flexographic, and 3D printing seem to be promising [72,73]. Printing techniques open new possibilities to customize dosage forms according to the individual's need for different patients, developing on-demand production methods, and incorporating multiple components into the same printing solution or multiple layers [10]. Also, there is an increase in the search for natural compounds as active ingredients, replacing the everyday use of synthetic drugs and encouraging ODFs of entirely natural composition.

Thus, we conclude that ODFs are a promising drug administration form, with increasing visibility in the market due to their excellent patient compliance and possibility of individual drug dosage. Nonetheless, the use of natural polymers opens excellent possibilities in developing ODFs, since they exhibit good film-forming properties, hydrophilicity, mucoadhesiveness, and, generally, good mechanical properties. Despite that, there is still place to investigate other natural polymers not explored yet, as well as alternative techniques to casting, such as printing technologies.

Acknowledgments

The authors thank the Coordination of Superior Level Personnel Improvement CAPES (finance code 001), National Council for Scientific and Technological Development (CNPq, grant #308994/2017-5), and São Paulo Research Foundation (FAPESP, grant #2018/25656-0) for financial support.

Declaration of competing interest

None.

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