



FEDERAL UNIVERSITY OF RIO GRANDE
SCHOOL OF CHEMISTRY AND FOOD
POSTGRADUATE PROGRAM IN FOOD ENGINEERING AND SCIENCE

DEVELOPMENT OF ORAL DISINTEGRATION FILMS AS VEHICLES FOR RELEASE
OF ASCORBIC ACID

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Thesis presented as a part of the
requirements to obtain the Doctoral
degree in Food Engineering and
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I dedicate this thesis to my parents, Antônio and Genoli, who were always with me, supporting and giving me all the support I needed, being my pillars of support and love.

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Unless we change our way of thinking, we will not be able to solve the problems
caused by the way we have become accustomed to seeing the world.

Albert Einstein

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CHAPTER I

GENERAL ABSTRACT

Oral disintegration films (ODFs) are thin films, composed of one or more soluble polymers that do not require water for their use, in addition to hydrating quickly when in contact with saliva, and have proven to be a new alternative for ingesting active compounds. The most used production method is the Casting technique due to its low cost and simplicity of production. Vitamin C, also known as ascorbic acid (AA), is water-soluble and is not produced or stored in the human body, making it necessary to ingest it through food or supplementation. It performs essential functions in the human body, combating the formation of free radicals, and has an oxidizing action, helping the body's cells to grow and stay healthy. The objective of the study was to develop orally disintegrating films added with different concentrations of vitamin C and evaluate their properties as well as their ability to support and release the active compound. The thesis was divided into three articles. In article I, a literature review was carried out on recent advances in ODFs as well as their applications and production methods used. Through the review, it was observed that orally disintegrating films have been an alternative for ingesting active compounds. Hydrophilic polymers are the most studied in the production of ODFs due to their ease of dissolution in contact with the oral mucosa. In article II, the polymer sodium alginate was studied, which has great application in the production of films but is still little used in ODFs. Because of its versatility and high solubility, alginate was used to produce ODFs added with different concentrations of vitamin C, evaluating its properties and capacity to support the active compound and its release. The films were homogeneous, with high solubility, disintegration time of less than 1 min, in addition to presenting a concentration of 80.46 mg.g⁻¹ in the formulation with 0.25% vitamin C, demonstrating that it is an alternative polymer as a carrier of active compound. Another extremely soluble and biodegradable polymer is methylcellulose, which is used in biodegradable films and also as reinforcement in blends as it improves their mechanical properties. It is still little explored in the production of ODFs. Article III studied the development of methylcellulose films added with different concentrations of vitamin C. In the study it was possible to observe that the polymer could incorporate the vitamin and also releasing the compound from the polymeric matrix. The films were soluble, with pH close to the oral pH, and short disintegration times, and the assessment of vitamin C concentration during the storage period was satisfactory since the formulation with 0.25% of vitamin had a concentration of 296.27 mg.g⁻¹ and for the formulation with 1% vitamin C the concentration was 556.53 mg.g⁻¹ and all formulations were above the recommended daily intake. Thus, the results of this study demonstrate that the polymers used are promising and have properties and characteristics that can be exploited in the production of oral disintegration films, in addition to being an alternative for ingesting vitamin C.

Keywords: Ascorbic acid; Polymers; Stability; Disintegration time.

RESUMO GERAL

DESENVOLVIMENTO DE FILMES DE DESINTEGRAÇÃO ORAL COMO VEÍCULOS PARA LIBERAÇÃO DE ÁCIDO ASCÓRBICO

Os filmes de desintegração oral (FDOs) são películas finas, compostos de um ou mais polímeros solúveis que não necessitam de água para sua ingestão. Estes se hidratam rapidamente quando em contato com a saliva e vem demonstrando ser uma nova alternativa para ingestão de compostos ativos. O método de produção mais utilizado é a técnica de *Casting* devido ao seu baixo custo e simplicidade de produção. A vitamina C também conhecida como ácido ascórbico (AA) é hidrossolúvel e não é produzida no corpo humano, sendo necessário a ingestão da mesma através da alimentação ou suplementação. Esta exerce funções essenciais no corpo humano, combatendo a formação de radicais livres e também possui ação oxidante ajudando as células do organismo a se manterem saudáveis. O objetivo do estudo foi desenvolver filmes de desintegração oral adicionados de diferentes concentrações de vitamina C e avaliar suas propriedades bem como a capacidade de suportar e liberar o composto ativo. A tese foi dividida em três artigos. No artigo I foi realizada uma revisão bibliográfica sobre os avanços recentes dos FDOs, suas aplicações e métodos de produção. Através da revisão foi observado que os filmes de desintegração oral vem sendo uma alternativa para a ingestão de compostos ativos. Polímeros hidrofílicos são os mais estudados na produção dos FDOs pela sua facilidade de dissolução. No artigo II foi estudado o polímero alginato de sódio, que tem grande aplicação na produção de filmes, porém ainda é pouco usado em FDOs. Tendo em vista sua versatilidade e sua alta solubilidade o alginato foi empregado para produção de FDOs adicionados de diferentes concentrações de vitamina C sendo avaliado as suas propriedades e a capacidade de suportar o composto ativo e sua liberação. Os filmes se apresentaram homogêneos, com alta solubilidade, tempo de desintegração inferior a 1 min além de apresentarem concentração de $80,46 \text{ mg.g}^{-1}$ na formulação com 0,25% de vitamina C, demonstrando ser uma alternativa de polímero como carreador do composto ativo. Outro polímero extremamente solúvel e biodegradável é a metilcelulose empregada em filmes biodegradáveis e também em blendas por melhorarem as propriedades mecânicas dos mesmos, sendo ainda pouco explorada na produção de FDOs. Portanto, o artigo III estudou o desenvolvimento de filmes de metilcelulose adicionados de diferentes concentrações de vitamina C. Foi possível observar que o polímero foi capaz de incorporar a vitamina além de liberar o composto da matriz polimérica. Os filmes se apresentaram solúveis, com pH próximo ao bucal, tempos de desintegração curtos e a avaliação da concentração de vitamina C durante o período de armazenamento se apresentou satisfatória sendo que a formulação com 0,25% de vitamina apresentou concentração de $296,27 \text{ mg.g}^{-1}$ e para a formulação com 1% de vitamina C a concentração foi de $556,53 \text{ mg.g}^{-1}$, sendo que todas as formulações se apresentaram acima da ingestão diária recomendável. Desta forma, os resultados deste estudo demonstram que os polímeros usados são promissores e com propriedades e características que podem ser exploradas na produção de filmes de desintegração oral, além de serem uma alternativa para ingestão de vitamina C.

Palavras-chave: Ácido ascórbico; Polímeros; Estabilidade; Tempo de desintegração.

1 GENERAL INTRODUCTION

Oral disintegration films (ODFs) have been highlighted as a new system for ingestion of active compounds, as they show good therapeutic adherence in children, elderly, and dysphagic people (BAO *et al.*, 2024; CASTRO *et al.*, 2018). Its formulation allows the active compound to be absorbed into the bloodstream through the oral mucosa, avoiding the effect of intestinal first-pass metabolism, and thereby improving the bioavailability of the compounds (SPEER *et al.*, 2018).

They present some advantages such as ease of swallowing, precise dosage, low thickness, flexibility, greater surface area of contact, ease of transport, greater comfort, and acceptability compared to oral products such as tablets, in addition to not requiring water for administration (MUSAZZI *et al.*, 2020; PALEZI *et al.*, 2023).

Studies have been developed using different polymers and active compounds such as for the treatment of cardiovascular diseases (CHUA; ADITYA; SHEN, 2012), Parkinson's (LAI *et al.*, 2018), fever and pain (TAKEUCHI *et al.*, 2018), anti-inflammatory prednisone (BRNIAK; MAŠLAK; JACHOWICZ, 2015) and also the growing interest in carrier systems for natural and bioactive compounds such as anthocyanins (BAO *et al.*, 2024), bioactive molecules (CASTRO *et al.*, 2018), Vitamin C (GARCIA *et al.*, 2018a; PALEZI *et al.*, 2023), ethanolic extract of propolis, and probiotics (HEINEMANN; CARVALHO; FAVARO-TRINDADE, 2013).

The most common methods for producing ODFs include the solvent *Casting* method (BRADY *et al.*, 2017; MUSAZZI *et al.*, 2020) and hot melt extrusion (DOUGLAS *et al.*, 2016; MUSAZZI *et al.*, 2020). Still, electrospinning and printing technologies have also been studied as alternative ways of producing ODFs (MUSAZZI *et al.*, 2020).

The choice of polymer is one of the most significant parameters for better and more effective film formation. Polymers can be used alone or in mixtures (blends) to obtain the desired properties in the film (BODINI *et al.*, 2019; KAPOOR, 2015). The polymers used in the preparation of ODFs must be non-toxic, non-irritating, low cost, low disintegration time, good spreadability, and free from impurities, in addition to being strong enough to avoid any physical damage during handling or transport (BODINI *et al.*, 2019; DIXIT; PUTHLI, 2009). Hydrophilic polymers are most used in the formation of ODFs because they are biocompatible, being structured at a molecular level and adapting better to the various active compounds used. Recently, natural polymers have also started to be used in ODF formulations (GARCIA *et al.*, 2018a; IRFAN *et al.*, 2016).

A polysaccharide used for film production is sodium alginate, a biodegradable and non-toxic polymer found in the cell walls of brown algae of the Phaeophyceae class. Sodium alginate films can be easily developed using the casting technique by solubilizing the polymer in water and subsequently drying (QIN *et al.*, 2017). Sodium alginate has hydroxyl and carboxyl groups that can create bonds with the mucin of the oral mucosa, which favors its dissolution, in addition to being a promising material in several industrial applications (BERGONZI *et al.*, 2020; CHEN *et al.*, 2017).

Methylcellulose (MC) is an ester derived from cellulose synthesized by alkaline treatment of cellulose followed by a reaction with methyl chloride. MC is a water-soluble hydrophilic biopolymer that presents thermal gelation property and ideal film formation capacity (KALKAN; OTAĞ; ENGIN, 2020; NASATTO *et al.*, 2015). They have been used in various industrial applications as a binder and disintegrant in tablets to achieve the controlled release of active compounds (BRADY *et al.*, 2017).

Vitamin C is a soluble solid that supports the immune system. It has a cyclic ester that is hydrolyzed in aqueous media to form acid, called ascorbic acid (LACHAPELLE; DROUIN, 2011). Ascorbic acid is an antioxidant that circulates in the bloodstream and neutralizes chemical substances that can damage tissues in the human body. Vitamin C protects the skin from the harmful effects of UV light and improves the strength of gums and teeth. Among vitamins, ascorbic acid is easily eliminated by oxidation and oxidized by exposure to air (JACOBS *et al.*, 2015; LACHAPELLE; DROUIN, 2011).

The human body is unable to synthesize this vitamin and cannot store it. Therefore, adequate amounts must be ingested, often through diet or supplements. In this context, the objective of this work was to develop and characterize orally disintegrating films produced from different polymers added of vitamin C as a new alternative for delivering the vitamin C.

2 INTRODUÇÃO GERAL

Os filmes de desintegração oral (FDOs) vêm se destacando como um novo sistema para administração de compostos ativos, por apresentarem boa adesão terapêutica em crianças, idosos e pessoas disfágicas (BAO *et al.*, 2024; CASTRO *et al.*, 2018). Sua formulação permite que o composto ativo seja absorvido pela circulação sanguínea através da mucosa oral, evitando o efeito do metabolismo de primeira passagem intestinal com isso melhorando a biodisponibilidade do compostos (SPEER *et al.*, 2018).

Esses filmes apresentam algumas vantagens como a facilidade de deglutição, dosagem precisa, baixa espessura, flexibilidade, maior área superficial de contato, facilidade de transporte, maior conforto e aceitabilidade em relação aos produtos orais como comprimidos, além de não necessitarem de água para sua ingestão (MUSAZZI *et al.*, 2020; PALEZI *et al.*, 2023).

Estudos têm sido desenvolvidos empregando diferentes polímeros e compostos ativos, utilizando esses filmes em tratamentos de doenças cardiovasculares (CHUA; ADITYA; SHEN, 2012), Parkinson (LAI *et al.*, 2018), febre e dor (TAKEUCHI *et al.*, 2018), anti-inflamatório prednisona (BRNIAK; MAŠLAK; JACHOWICZ, 2015), e também vem crescente o interesse em sistemas carreadores de compostos naturais e bioativos como antocianinas (BAO *et al.*, 2024), moléculas bioativas (CASTRO *et al.*, 2018), Vitamina C (GARCIA *et al.*, 2018a; PALEZI *et al.*, 2023), extrato etanólico de própolis, e probióticos (HEINEMANN; CARVALHO; FAVARO-TRINDADE, 2013).

Os métodos mais comuns de produzir FDOs incluem o método de fundição por solvente (LEE *et al.*, 2017; MUSAZZI *et al.*, 2020) e extrusão de fusão a quente (DOUGLAS *et al.*, 2016; MUSAZZI *et al.*, 2020). Ainda assim, tecnologias de eletrofição e impressão 3D também têm sido estudadas como formas alternativas de produzir FDOs (MUSAZZI *et al.*, 2020).

A escolha do polímero é um dos parâmetros mais significativos para uma melhor e eficaz formação do filme. Os polímeros podem ser utilizados sozinhos ou em blendas para se obter propriedades desejadas no filme (BODINI *et al.*, 2019; KAPOOR, 2015). Os polímeros empregados na preparação dos FDOs devem ser não tóxicos, não irritantes, ter baixo custo, baixo tempo de desintegração, boa espalhabilidade, ser isentos de impurezas, além de serem fortes o suficiente para evitar qualquer dano físico durante o manuseio ou transporte (BODINI *et al.*, 2019; DIXIT; PUTHLI, 2009). Os polímeros hidrofílicos são os mais empregados na formação dos FDOs por serem biocompatíveis, se adaptando melhor com os vários compostos

ativos empregados. Recentemente polímeros naturais como também passaram a ser utilizados nas formulações dos FDOs (GARCIA *et al.*, 2018a; IRFAN *et al.*, 2016).

Um polissacarídeo utilizado para produção de filmes é o alginato de sódio, sendo um polímero biodegradável e não tóxico, encontrado nas paredes celulares de algas marrons da classe Phaeophyceae. Filmes de alginato de sódio podem ser facilmente desenvolvidos a partir da técnica de *Casting* através da solubilização do polímero em água e posterior secagem (QIN *et al.*, 2017). O alginato de sódio possui grupos hidroxilas e carboxilas que podem criar ligações com a mucina da mucosa bucal o que favorece a sua dissolução, além do que vem se mostrando um material promissor em várias aplicações industriais (BERGONZI *et al.*, 2020; CHEN *et al.*, 2017).

A metilcelulose (MC) é um éster derivado da celulose sintetizado por tratamento alcalino da celulose seguido de reação com cloreto de metila. MC é um biopolímero hidrofílico solúvel em água que apresenta propriedade de gelificação térmica e capacidade ideal de formação de filme (KALKAN; OTAĞ; ENGIN, 2020; NASATTO *et al.*, 2015). Este vem sendo utilizados em várias aplicações industriais como aglutinante e desintegrante em comprimidos para alcançar a liberação controlada de compostos ativos (BRADY *et al.*, 2017).

A vitamina C é um sólido solúvel que auxilia no sistema imunológico, esta possui um éster cíclico que é hidrolisado em meio aquoso para formar um ácido, sendo chamado de ácido ascórbico (LACHAPELLE; DROUIN, 2011). O ácido ascórbico é um antioxidante que circula na corrente sanguínea e neutraliza substâncias químicas que podem danificar tecidos do corpo humano. A vitamina C protege a pele de efeitos nocivos da luz UV, melhora a força de gengivas e dentes. Dentre as vitaminas, o ácido ascórbico é facilmente eliminado pela oxidação, podendo ser oxidado pela exposição ao ar (JACOBS *et al.*, 2015; LACHAPELLE; DROUIN, 2011). O corpo humano é incapaz de sintetizar esta vitamina e não pode armazená-la. Portanto, quantidades adequadas devem ser ingeridas, através da dieta ou suplementos. Neste contexto o objetivo deste trabalho foi desenvolver e caracterizar filmes de desintegração oral produzidos a partir de diferentes polímeros adicionados de vitamina C como uma nova alternativa de consumo de vitamina C.

3 OBJECTIVES

3.1 GENERAL OBJECTIVE

Develop and characterize orally disintegrating films from different polymers added with vitamin C as a new active compound delivery alternative.

3.2 SPECIFIC OBJECTIVES

- Produce and evaluate sodium alginate films added with different concentrations of vitamin C.
- Produce and evaluate methylcellulose films added with different concentrations of vitamin C.
- Evaluate the interaction between the studied polymers and vitamin C.
- Analyze the release of vitamin C through the polymeric matrices used.
- Evaluate the stability of films stored at different temperatures.

CHAPTER II

4 LITERATURE REVIEW

4.1 ORAL DISINTEGRATION FILMS

Oral disintegrating films (ODF) have been studied in recent years as a new way of ingesting active compounds. Oral disintegration films, also called rapid disintegration films, oral films, orodispersible films, are thin films that disintegrate quickly when in contact with the oral mucosa, releasing the active compound (GARCIA *et al.*, 2020b; PACHECO *et al.*, 2021).

The thickness of ODFs can vary between 50 and 500 μm and the surface area between 1 and 20 cm^2 , depending on the dose of active ingredient and the location to which it will be applied. They need to be flexible, however, they must be resistant to handling and transportation, they must remain flat, without curling after production (BALA *et al.*, 2013).

The use of oral disintegration films as a vehicle for active compounds has aroused interest, mainly due to some advantages, such as ease transportation, they do not require chewing and have rapid dispersion in the oral mucosa due to the action of saliva. The films release the active ingredient in the oral cavity, being ease of swallowing for geriatrics and pediatrics, also allow flexibility and customization of doses, aiming to achieve local or systemic action, with rapid onset of action. Furthermore, they do not require water for administration, making them convenient for dysphagic patients with difficulty swallowing tablets and capsules (BALA *et al.*, 2013; BORGES; DE CARVALHO, 2015; IRFAN *et al.*, 2016).

Oral disintegration films are mainly made up of macromolecules capable of forming a polymeric matrix, plasticizing agent, and the active compound of interest (BORGES; DE CARVALHO, 2015; TEDESCO; MONACO-LOURENÇO; CARVALHO, 2017). Natural and synthetic polymers can be used in the production of films and in different compositions in order to achieve the desired properties of the product (KARKI *et al.*, 2016). The choice of the macromolecule is the first step in the development of these materials, as it is responsible for providing important characteristics to the films, such as, good handling and high hydrophilicity to facilitate dissolution in the oral cavity (TEDESCO; MONACO-LOURENÇO; CARVALHO, 2016).

Therefore, films can present different characteristics depending on the components used for their production. In the literature, oral films with different characteristics can be found, such as films with a long disintegration time (STEINER; FINKE; KWADÉ, 2016), rapid disintegration (GARCIA *et al.*, 2020a; MAZUMDER *et al.*, 2017; TAKEUCHI *et al.*, 2019) in addition to mucoadhesives and controlled release (PORNPICHANARONG *et al.*, 2020).

Among the forms of administration of active compounds, the oral mucosa is the most acceptable and convenient for patients due to its ease of administration, adaptability, and acceptability by the patient (DIXIT; PUTHLI, 2009; IRFAN *et al.*, 2016). Oral disintegration films, as they are administered orally (by sublingual, buccal and palatal administration), do not subject the active ingredient incorporated into the film to degradation by first-pass metabolism through the action of liver enzymes, leading to its elimination, which can prevent that desired therapeutic levels are reached (TAKEUCHI *et al.*, 2019).

ODFs have some disadvantages, such as not being possible to choose active ingredients that may undergo degradation, those that may be irritating to the oral mucosa or that have a very bitter taste, as they release the active ingredient into the oral cavity. The administration of active compounds in high doses is not yet possible due to their low thickness (BORGES; DE CARVALHO, 2015; KARKI *et al.*, 2016).

The choice of preparation method is a limiting factor to produce ODFs, in order to ensure that dose uniformity is achieved. In addition, they are relatively fragile, requiring care in choosing packaging and appropriate storage conditions. Humidity is the main factor that triggers instability in its composition, which can lead to sticky films, in addition to favoring the hydrolysis of the active compound (BALA *et al.*, 2013; TAKEUCHI *et al.*, 2019).

4.2 POLYMERS USED TO PRODUCE ORAL DISINTEGRATING FILMS

Polymers are essential and major components in the production of ODFs, as they need to guarantee characteristics such as easy disintegration and physical resistance to the film. Natural and synthetic polymers can be used in the production of orally disintegrating films and different compositions can be used in order to achieve the desired properties of the product (KARKI *et al.*, 2016).

Dixit and Puthli (2009) highlighted some characteristics that the polymers used for the development of orally disintegrating films must present, such as: being free of impurities, cheap and easily available, being non-toxic, non-irritating, not being bitter, having a short time of disintegration and must not cause irritation to the oral mucosa. According to Kumar *et al.* (2011) hydrophilic polymers are widely used in the production of orally disintegrating films, as they disintegrate quickly and the incorporated compounds are released into the oral cavity when they come into contact with saliva.

4.2.1 Alginate

Alginates are salts of alginic acid, natural polysaccharides from brown algae of the Phaeophyceae family. They are copolymers whose structure consists of (1 → 4) monomers of β -D-mannuronic acid (M) and α -L-glucuronic acid (G) glycosidically linked in similar or alternating sequences or covalent blocks (MMMM, GGGG or GMGM). The proportion and distribution of these blocks depend on the alginate source and determine the properties of the biopolymer (LEE; MOONEY, 2012).

Alginates have applications in food, medicine, environmental protection fields, and packaging. Due to their swelling and gelling properties, alginates have been used as controlled-release agents in pharmaceutical formulations (GUO *et al.*, 2020). It has been applied in ODF formulations as a film-forming agent or combined with other polymers.

The Food and Drug Administration (FDA), specifies food-grade sodium alginate as a GRAS substance (generally considered safe), in addition to listing its use as an emulsifying, stabilizing, thickening, and gelling agent (FDA, 2020).

Alginate films have been attracting commercial interest because they have good flexibility, are soluble in water, have emulsification capacity, shine, have no odor or taste, and have low permeability to oil and oxygen (PAIXÃO *et al.*, 2019). Alginate-based ODFs showed high tensile strength and high hydrophilicity with disintegration time within 60 s (EL-BARY; AL SHARABI; HAZA'A, 2019).

4.2.2 Methylcellulose

Methylcellulose is a cellulose ester obtained by treating cellulose with alkali, followed by reaction with methyl chloride. Methylcellulose, exhibits thermal gelation, has ideal film-forming properties and is commonly used as a vehicle for antimicrobial agents in the production of edible films (SONG *et al.*, 2010). The use of methylcellulose in the production of biodegradable polymers has been researched, due to its excellent film-forming properties and high solubility, in addition to the fact that it can be used as a reinforcing material, increasing mechanical properties (DING; ZHANG; LI, 2015a).

Methylcellulose is recognized as safe (GRAS - Generally Recognized as Safe) by the FDA and Anvisa when used as a food additive and is approved for use in dietary supplements, foods and as a component in over-the-counter medicines (FDA, 2022).

Methylcellulose films, in general, present high transparency, absence of aromas and taste, flexibility, good barrier to oil and fat and have moderate oxygen transmission (NORONHA *et al.*, 2014). In addition to their protective barrier, methylcellulose films have been used to provide a containment and release mechanism for active compounds, which act as natural additives in films (KALKAN; OTAĞ; ENGIN, 2020).

In the food industry, this input is widely used due to its gel-forming properties that act as stabilizers, emulsifiers and thickeners that contribute to the control of syneresis, crystal size, and retention of particles in suspension in food production (LI; NIE, 2016).

4.3 PRODUCTION AND COMPOSITION OF ORAL DISINTEGRATION FILMS

The most used methods for producing oral disintegration films are extrusion and casting techniques. The printing and tape casting technique has also been studied as alternatives for producing ODFs.

The casting technique called solvent evaporation method is most used for the production of orally disintegrating films due to its simplicity and low cost (MUSAZZI *et al.*, 2020). In this technique, polymers, active compounds, and other additives are solubilized in a suitable solvent and can be subjected to stirring and heating for solubilization (KUMAR *et al.*, 2017). The solution obtained goes through a drying process and then the film formed can be cut to the desired size (NIESE; QUODBACH, 2019). Depending on the thickness and size of the film formed, the dose of the drug or active compound that can be carried is determined (MUSAZZI *et al.*, 2018). There are several studies found in the literature that report the casting technique as a method of producing ODFs.

In the extrusion technique, the polymer and other ingredients are mixed in a dry state, subjected to a heating process, and then extruded. Solvents are completely eliminated in this process (DIXIT; PUTHLI, 2009). However, the technique for producing oral disintegration films using the extrusion process is little reported in the literature, despite presenting some characteristics such as better uniformity of drug content and reduced operational units (ARYA *et al.*, 2010).

The production of oral disintegration films, in general, uses polymers, plasticizers and active compounds, which can be of natural or synthetic origin, and may use other ingredients such as saliva stimulating agent, surfactant, sweetener and flavorings to attribute the properties desired films (PATEL; PRAJAPATI; RAVAL, 2010; SAINI *et al.*, 2012).

Plasticizers are considered extremely important ingredients for the production of orally disintegrating films, as they improve the flexibility and reduce the fragility of ODFs. The selection of the type of plasticizer used in orally disintegrating films will depend on compatibility with the polymer and the type of solvent used (PATEL; PRAJAPATI; RAVAL, 2010). The plasticizers selected to produce orally disintegrating films, glycerol, and polyethylene glycol, are the most used.

Polymer selection for the development of oral film matrices is a critical step and can vary taking into account the profile of the target product. When choosing the polymer, its affinity with the active compound of interest and the mechanical properties of the films must be considered, as the film must be resistant enough to be handled and transported without being damaged, in addition to keep the active compound stable until it is removed released (BORGES; DE CARVALHO, 2015; MUSAZZI *et al.*, 2018).

Disintegration films are used to incorporate various compounds, which is a determining factor for their functionality. In this sense, the number of research in this area has been increasing, as can be seen in Table 1, which lists oral disintegration films with different active compounds and therapeutic functionalities.

Table 1 – Example of studies related to the production of oral disintegration films with the incorporation of active ingredients.

Category	Polymer	Active compounds	Form of production	Reference
Oral disintegration film	Hydroxypropylmethylcellulose (HPMC) and crospovidone	Rasagiline mesylate	Tape-casting + printing	Janssen <i>et al.</i> (2013)
	Polyvinyl alcohol and carboxymethylcellulose	Clonidina		Buanz <i>et al.</i> (2015)
	Gelatin	Propolis ethanolic extract	Casting	Borges; De Carvalho (2015)
	Starch and gelatin	Acerola dry extract		Garcia <i>et al.</i> (2017)
	HPMC and gelatin	Peanut shell extract		Tedesco; Monaco-Lourenço; Carvalho (2017)
Mucoadhesive films	Gelatin and chitosan	Propranolol	Casting	Abruzzo <i>et al.</i> (2012)

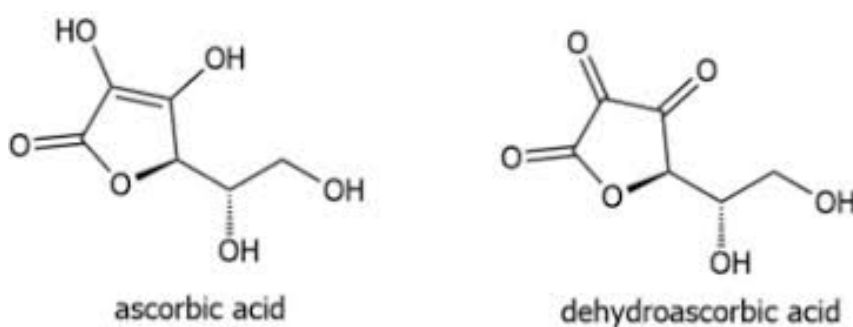
HPMC, chitosan, sodium hyaluronate, and gelatin	Ondansetron		(TRASTULLO <i>et al.</i> , 2016)
HPMC, sodium alginate	Nicotine		(OKEKE; BOATENG, 2017)
HPMC e Soluplus®	Ketoconazole	Hot extrusion	Maniruzzaman <i>et al.</i> (2016)
HPMC e PEO N750	Domperidone		Palem <i>et al.</i> (2016)

4.4 ASCORBIC ACID

Vitamins are a class of nutrients essentially required by the body for its various biochemical and physiological processes. Vitamins are subdivided into fat-soluble and water-soluble. Fat-soluble vitamins are those soluble in lipid solvents, such as vitamins A, D, E and K. Water-soluble vitamins are soluble in water, such as vitamins C and B (IQBAL; KHAN; KHATTAK, 2004).

Vitamin C is also known as ascorbic acid, L-ascorbic acid, dehydroascorbic acid, ascorbate, and antiscorbutic vitamin (VANNUCCHI; ROCHA, 2012). Ascorbic acid (AA) is a compound that corresponds to an oxidized form of glucose (C₆H₈O₆) with a molecular weight of 176.13 g/mol, being an alpha-ketolactone with six carbon atoms, forming a lactone ring with five members and a group bifunctional enediol with an adjacent carbonyl group (VANNUCCHI; ROCHA, 2012). L-ascorbic acid and dehydroascorbic acid are the main dietary forms of vitamin C (Figure 1).

Figure 1 - Chemical structure of ascorbic acid



Source: Stevanović and Uskoković (2009).

Vitamin C has relevant functions in the body such as the formation of cartilage, collagen, muscles, and blood veins, an antioxidant agent, in addition to acting as a cofactor for many enzymes and acts efficiently in the elimination of reactive oxygen species (HAZA *et al.*, 2009). It has a protective function against cancer (HAZA *et al.*, 2009) with safely toxic activity for some types of tumor cells, also inducing apoptosis in leukemic cells (PARK *et al.*, 2004).

The human body needs vitamin C for its physiological functions, helping in the metabolism of tyrosine, folic acid, and tryptophan. It can lower blood cholesterol levels and contribute to the synthesis of amino acids, such as carnitine and catecholamine, which regulate the nervous system. They are essential for tissue growth and wound healing. It acts as an adjuvant in the formation of neurotransmitters and increases iron absorption in the intestine (IQBAL; KHAN; KHATTAK, 2004; PULLAR; CARR; VISSERS, 2017). Therefore, low vitamin C intake has been associated with the development of cardiovascular diseases, hypertension, stroke, diabetes mellitus, cancer, and Alzheimer's disease (LIU, 2009).

Since vitamin C cannot be synthesized or stored in humans, adequate amounts must be supplied through the diet. The National Health Surveillance Agency (ANVISA) recommends a daily intake of 45mg/day for adults. This vitamin is widely used in the food, cosmetics, and pharmaceutical industries as it can promote collagen synthesis (FINDIK *et al.*, 2016).

4.5 ACTIVE COMPONENTS - ABSORPTION MECHANISMS

The absorption of components and nutrients can be carried out via two routes: transdermal and transmucosal (HEARNDEN *et al.*, 2012). The most studied transmucosal routes include the lung, gastrointestinal, vaginal, rectal, ocular, and buccal tissues, with the rectal, vaginal and ocular mucosa being the routes with the least acceptance by patients. Furthermore, they are mainly restricted to the release of drugs for local diseases (HEARNDEN *et al.*, 2012).

The oral mucosa is a very vascularized region, which facilitates the absorption process of active compounds. Absorption can occur both via the sublingual route (region below the tongue) and via the buccal route (lateral region of the oral cavity), with the sublingual region being the most permeable (KUMAR; JHADE, 2017; SHIRVAN; BASHARI; HEMMATINEJAD, 2019). This absorption can occur in two ways: intracellularly (inside the cells) or extracellularly (outside the cells). Oral administration has gained prominence as it allows administration to people with difficulty swallowing, nausea, and vomiting (MORALES; MCCONVILLE, 2011).

The compound, when absorbed in the oral cavity, avoids passage through the entire gastrointestinal tract, thus avoiding degradation due to enzymatic action and pH variations, in addition to avoid first-pass metabolism, ensuring greater stability of the component and increasing its bioavailability (HEARNDEN *et al.*, 2012)

CHAPTER III

5 WORK OVERVIEW

The thesis was developed at the Laboratory of Food Technology (LTA), which is part of the School of Chemistry and Food Engineering (EQA) at the Federal University of Rio Grande (FURG) in partnership with other laboratories at the institution.

The results of the work were divided into three articles, which are described below.

Article 1: Oral disintegration films: applications and production methods.

Article 2: Orally disintegrating films based on sodium alginate as a carrier vehicle for vitamin C.

Article 3: Development and characterization of orally disintegrating methylcellulose films containing vitamin C.

6 PRELIMINARY TESTS

Oral disintegrating films (ODFs) are an innovative way of administering active compounds that disintegrate quickly in the mouth without the need of water (GARCIA et al., 2020a). For the development of the films, preliminary tests were carried out to evaluate the film formation capacity of different polymers, concentration of polymer to be used, concentration of the active compound that could be added to the polymeric matrix, its capacity of solubilization and formation of films that can be handled. Another property tested was the solubility of the polymers, which for these films is an important property as they needed to be soluble and dissolve quickly.

Oral disintegration films present some difficulties in their development due to their thinner thickness, which does not support high concentrations of active compounds.

The polymers sodium alginate, methylcellulose and bovine and porcine gelatin were tested, in different concentrations (m/v). The polymer concentrations tested were based on work already carried out by the laboratory's research group and existing literature.

The three polymers were able to form films and solubilize the active compound tested. However, for gelatin (bovine and porcine), the films were very hygroscopic, making handling difficult. When removing the films from the plates, they became tangled, making it impossible to carry out analyses. Sodium alginate and methylcellulose produced polymers suitable to be applied as ODFs and it is chosen for the development of this thesis.

Regarding the active compounds to be added to the films, vitamin C and some minerals such as iron, copper, calcium and magnesium were tested. Vitamin C was easily solubilized in alginate and methylcellulose matrices. It was then tested how much concentration could be added to the film-forming solution and whether it could form a film. Concentrations of 0.25, 0.5, 1, 1.5 and 2% (m/v) were tested, and solubilization was not possible at concentrations of 1.5 and 2%.

Regarding minerals, iron, copper, calcium and magnesium were tested in alginate and methylcellulose matrices. There are few reports of the addition of synthetic minerals to orally disintegrating films in the literature, with the initial concentration added based on the recommended daily intake. Then, two different concentrations were tested to observe the presence of the mineral in the film as well as its present concentration.

The mineral magnesium was tested at concentrations of 0.7 and 1.8% (m/v). When added to the methylcellulose matrix, it did not form films, since it did not completely dissolve

in any of the added concentrations. When added to the sodium alginate matrix in the two concentrations evaluated, the films formed were very brittle, making manipulation unfeasible.

For the mineral calcium, the concentrations tested were 1 and 2% (m/v). In both matrices it was not possible to dissolve the mineral in the film-forming solution, there was no compatibility between polymers and active compound.

The concentration of iron mineral tested was 0.7% (m/v) also based on the Recommended Daily Intake by FAO. In the methylcellulose matrix it was not possible to form a film, whereas in the sodium alginate matrix it was possible to form a film, and it was intact, without bubbles, tears and easy removal from the plate, however it was not possible to mask the bitter taste of the iron which would make its consumption unfeasible. When evaluated by the flame atomic absorption spectrometry method, the amount of iron found in the film was very low, almost zero, making its production not viable.

The copper mineral was tested at a concentration of 0.2% (w/v), based on the Recommended Daily Intake (RDI). In the alginate matrix, it was possible to obtain an intact film that was easy to remove from the plate. When flame atomic absorption spectrometry analysis was carried out, a very low concentration, almost zero, was obtained, discarding the idea of producing films. As for the methylcellulose matrix, it was not possible to form a manageable film, as they presented high hygroscopicity.

ARTICLE I

ORAL DISINTEGRATION FILMS: APPLICATIONS AND PRODUCTION METHODS

PALEZI, S. C.; FERNANDES, S. S.; MARTINS, V. G. Oral disintegration films: Applications and production methods. **Journal of Food Science and Technology**, v. 60, 2022.

Oral disintegration films: Applications and production methods

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.

Keywords: Orodispersible films; Active compounds; Edible polymers; Methods of production; Applications.

1 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; 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 (MUSAZZI *et al.*, 2020; THAKUR *et al.*, 2019).

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; 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 (CAROLINA VISSER *et al.*, 2017a; SCARPA *et al.*, 2017a), geriatricians (SLAVKOVA; 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; 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; MONACO-LOURENÇO; CARVALHO, 2016a).

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.

2 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; DE CARVALHO, 2015).

Oral 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; BREITKREUTZ; SANDLER, 2015).

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

Films such as “adhesives (adhesives)” adhere to the mucosa and remain for hours releasing the active compound (JANI; PATEL, 2014). After the release ends, the film must be removed (JANI; PATEL, 2014). These films are produced in multilayers, usually with insoluble or low-solubility polymers (BHATTARAI; GUPTA, 2016).

Garcia *et al.* (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.

Properties	Characteristics of ODFs			
	Quick ODFs	release	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)	(upper	Gingival or buccal region	Gingival (another region of the oral cavity)
Disintegration time	Less than 60 seconds		In a few minutes	Maximum 8 - 10 h
Action location	Systemic or local		Systemic or local	Systemic or local

Source: Garcia (2016).

Pharmaceutical company Pfizer developed the first commercial oral film that was named “Listerine® pocket packs™” 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.

Table 2 - Examples of commercial oral films.

Commercial name	Active principle	Functionality
Niquitin Strips®	Nicotine	Help to stop smoking
Sumnulent ®	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

3 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.

Table 3 - Main compounds used in the production of oral disintegration films.

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.*

Source: Singh *et al.* (2018b)

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; 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 (ALHAYALI; VUDDANDA; VELAGA, 2019; BALA; SHARMA, 2018; IRFAN *et al.*, 2016).

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).

3.1 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; VUDDANDA; VELAGA, 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).

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; VUDDANDA; VELAGA, 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; JAIPAKDEE, 2020), chitosan (VERMA; RAJPUT; NAIK, 2018), gelatin (BORGES; 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; 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 (SINGH *et al.*, 2018b; TEDESCO; MONACO-LOURENÇO; CARVALHO, 2016b). 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.

3.2 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 ODFs, large doses are difficult to be incorporated, generally containing only 5 to 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; SHEELA, 2015), fluoxetine antihistamine (CHEVALA *et al.*, 2015) and prednisone anti-inflammatory (BRNIAK; MAŠLAK; JACHOWICZ, 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; BREITENBACH; BREITKREUTZ, 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.

Table 4 - Examples of active ingredients incorporated in oral disintegration films.

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

4 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 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 (ALAEI; OMIDIAN, 2021; LAI *et al.*, 2018; LAM *et al.*, 2014b).

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; 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 (HUA, 2019; LAI *et al.*, 2018).

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; PARK, 2020).

5 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.

5.1 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; 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 (BODINI *et al.*, 2020; BORGES; DE CARVALHO, 2015; MA *et al.*, 2015; SINGH *et al.*, 2018a; VERMA; RAJPUT; NAIK, 2018).

5.2 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; 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).

5.3 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 ODFs 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 ODFs 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.

5.4 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; DODOO *et al.*, 2020; SCARPA *et al.*, 2017b; VUDDANDA *et al.*, 2017). 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; BREITKREUTZ; SANDLER, 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; GARCIA; DE CARVALHO, 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; BREITKREUTZ; SANDLER, 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, 30min 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.

6 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; 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.

Table 5. Application of some orodispersable films.

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

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 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 seconds.

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.* (2020a) 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 $166.7 \pm 3.30 \mu\text{m}$, tensile strength $38.45 \pm 3.72 \text{ MPa}$, elongation $23.38 \pm 4.23\%$ and bending strength > 200 times), and its time of disintegration was about $18 \pm 1.23 \text{ s}$.

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 ($\sim 98\%$) 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 $\bullet+$ and FRAP of 3.68 ± 0.23 and $14.61 \pm 0.66 \text{ mMol ET/g OF}$, and total phenolic content of $3.55 \pm 0.27 \mu\text{mol GAE/g OF}$, 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.

7 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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ARTICLE II

ORALLY DISINTEGRATING FILMS BASED ON SODIUM ALGINATE AS A CARRIER VEHICLE FOR VITAMIN C

PALEZI, S. C.; FERNANDES, S. S.; BARBOSA, S. C.; PRIMEL, E. G.; MARTINS,
V. G. Orally disintegrating films based on sodium alginate as a carrier vehicle for vitamin C.
International Journal of Food Science and Technology, v. 59, 2024.

Orally disintegrating films based on sodium alginate as a carrier vehicle for vitamin C

ABSTRACT

Orally disintegrating films (ODFs) have been studied for their innovative way of delivering active compounds into the oral cavity. The study aimed to develop and evaluate ODFs using sodium alginate and different concentrations of vitamin C. Four formulations were evaluated for barrier, mechanical, thermal, microstructural properties, surface pH, disintegration time and concentration of vitamins. The ODFs produced showed high solubility, pH close to oral, and disintegration time ranging from 24.66 s for the control formulation to 56.28 s for the 1% ascorbic acid formulation. The release of vitamin C occurred after 1 min of reaction for all formulations with the lowest concentration (0.25%) releasing a volume of 80.46 mg.g⁻¹. Thermal analyses demonstrated the presence of sodium alginate and vitamin C, and interaction between them, confirmed by FTIR spectra. This interaction was interesting for ODFs since it can affect the properties and release of the active compound from the polymeric matrix. The results were positively demonstrated that sodium alginate can be a promising polymer in the production of ODFs and for use in the delivery of vitamin C.

Keywords: Ascorbic acid; Edible films; Thermal analysis; FT-IR; HPLC.

1 INTRODUCTION

Orally disintegrating films (ODFs) have gained prominence in the area of functional foods and the supplementation of active compounds due to their characteristics of providing these compounds orally (PEZIK *et al.*, 2021). ODFs are thin in thickness, flexible in shape, easy to handle and transport, accurate in dosage, and are a good alternative for adults, children, and people with swallowing difficulties (LAI *et al.*, 2018; LIMPONGSA; JAIPAKDEE, 2020). The rapid disintegration time when in contact with saliva in the oral cavity is one of its main characteristics (TAKEUCHI *et al.*, 2018).

Currently, ODFs are being studied by several researchers, as they are promising as vehicles for the release of active compounds, such as in the fight against pain and fever (TAKEUCHI *et al.*, 2018), Parkinson's (LAI *et al.*, 2018) and also for antimicrobial and antioxidant activity (BODINI *et al.*, 2020; GARCIA *et al.*, 2018b). There is also a growing interest in the use of ODFs as carriers of natural and bioactive compounds, such as propolis ethanolic extract, probiotics (HEINEMANN; CARVALHO; FAVARO-TRINDADE, 2013), and vitamin C (GARCIA *et al.*, 2018a).

Numerous polymers can be used in the production of ODFs since they can be used alone or in blends to achieve the desired properties (BODINI *et al.*, 2020). Sodium alginate is extracted from brown algae (Phaeophyta) and is considered a natural biopolymer, it has been studied as a promising material with several industrial applications as in the pharmaceutical industry in alginate-based drugs for diabetes control (SHAIKH *et al.*, 2023), tablet disintegrants (BERARDI *et al.*, 2021) and membranes (PACHECO *et al.*, 2020), in the food sector, as stabilizer (ZHANG *et al.*, 2023) and encapsulating materials (MAZZA *et al.*, 2023).

Alginate has different properties such as good biocompatibility, biodegradability, non-toxic nature, and low cost. In addition, it has several hydroxyl and carboxyl groups, which allows its binding to mucin in the oral mucosa, making it a suitable polymer for application in ODFs. Several studies are reporting the use of sodium alginate in the production of edible films (ZHOU *et al.*, 2022), anti-microbial films (NAZIR; WANI, 2022), multi-component films (YUAN *et al.*, 2022), and bioadhesive films, but there are still few studies for its application in ODFs, in addition to being able to withstand higher dosages of the active principle.

Ascorbic acid (AA) or vitamin C, is a water-soluble vitamin, representing a structural and diverse set of functional organic molecules, playing an important role in maintaining cellular metabolism and energy (ABD EL AZIM *et al.*, 2015). Human beings are unable to synthesize vitamin C, therefore, it is necessary to ingest food or supplements that contain it (HUANG *et al.*, 2022) with a recommended daily intake of 45 mg.d⁻¹ as quoted by the World Health Organization (WHO). The study aimed to develop an ODF using sodium alginate added to different concentrations of vitamin C as a new alternative vehicle for delivering active compounds.

2 MATERIAL AND METHODS

2.1 MATERIALS

Sodium alginate and glycerol were purchased from Êxodo Científica (Sumaré, Brazil). Vitamin C was purchased from Sigma-Aldrich (São Paulo, Brazil). The chemical reagents used were all analytical grades.

2.2 FILMS PRODUCTION

The films were produced as described by Oliveira Filho *et al.* (2019) using the casting technique, with some adaptations. To obtain the filmogenic solution, sodium alginate 1.5%

(w/v) and the plasticizer glycerol 35% (w/w) were used, solubilized in distilled water in a jacketed reactor at 70 °C for 1 h. The solution was cooled to 30 °C and 0.25, 0.5, and 1% (w/v) concentrations of AA were added. These concentrations were obtained through preliminary tests following the methodology of Garcia *et al.*, (2018a). A film without the addition of AA was produced as a control. After homogenization, 20 g of the solution was placed in Petri dishes ($\varnothing = 9$ cm) and dried at 30 °C for 24 h in an air circulation oven (Q316M - Quimis, Brazil). The film without addition of AA was denominated CF and the films added with 0.25, 0.5, and 1% (w/v) of AA were denominated F1, F2, and F3, respectively.

2.3 MECHANICAL CHARACTERIZATION AND BARRIER PROPERTIES OF FILMS

The thickness was measured at ten different positions on the film using a micrometer (IP54 - Insize, Brazil). The mechanical properties of tensile strength (MPa) and elongation at break (%) were analyzed using standard method D-882-02 (ASTM, 2013) and determined with a texture analyzer (TA. XTplus - Stable Micro Systems, England). The films ($n = 10$) were cut into strips (50 × 25 mm) and the test was carried out with an initial adhesion separation of 50 mm and a head speed of 1 mm.s⁻¹.

Water solubility (%) was determined according to Gontard *et al.* (1994). The films were placed in an aluminum capsule, dried at 105 °C in an oven (A15-E - DeLeo, Brazil) to determine the dry weight of the film (wi), after which the films were submerged in 50 mL of distilled water and shaken in orbital shaker (TE 420 - Tecnal, Brazil) at 150 rpm for 24 h. The insoluble materials were dried at 105°C for 24 hours and the final dry film weight (wf) was determined. Water solubility was calculated as the ratio between wi and wf.

Water vapor permeability (WVP) was measured gravimetrically according to standard method E96-00 (ASTM, 2013). To carry out the analyses, plastic containers, silica gel, and film samples were used. The films were stored in a desiccator at 75% RH and the containers were weighed for 7 days every 24 h, the WVP being determined by Equation 1.

$$\text{WVP (g mm kPa}^{-1} \text{ day m}^{-2}) = \frac{W \cdot L}{A \cdot t \cdot \Delta P} \quad (1)$$

Where: W silica mass gain (g), L film thickness (mm), A permeation area (m²), t mass gain time (day) and ΔP vapor pressure difference between the film (kPa) respectively.

2.4 SURFACE pH

The surface pH was evaluated according to Prabhu *et al.* (2011) using phosphate buffer pH=6.75, to simulate saliva, prepared according to Wong; Yuen; Peh, (1999). Strips of ODFs (3 cm x 2 cm) were placed in contact for 30 seconds with 0.5 mL of buffer solution and after 1 min the pH was determined using a bench pH meter (Q400AS).

2.5 DISINTEGRATION TIME

The disintegration time was determined according to Perumal *et al.* (2008). Film samples (3 x 2 cm) were diluted in 50 mL of phosphate buffer solution under agitation of 100 rpm.min⁻¹ at 37 °C in an orbital shaker (TE 420 - Tecnal, Brazil). The disintegration time was determined as the time required (min) for the sample to completely dissolve. Samples were analyzed in triplicate.

2.6 SCANNING ELECTRON MICROSCOPY (SEM)

Scanning electron microscopy (SEM) was performed on the surface and cross-sectional area of the films using a microscope (JSM-6610LV, Jeol). Before analysis, film samples were stored in desiccators containing silica gel for 7 days. After this period, the films were fixed on aluminum stubs and covered with gold, and microphotographs were taken with magnifications of 1.000 times for the surface and 500 times for the cross-section area, and the beam voltage used was 10 kV. For cross-sectional analysis, the films were fractured with liquid nitrogen.

2.7 FOURIER TRANSFORM-INFRARED SPECTROSCOPY (FTIR)

FTIR analysis was performed to determine chemical functional groups and possible interactions in the samples. Characterization was by Fourier transform infrared spectroscopy using a Prestige-21 IR spectrophotometer (Shimadzu), forty scans were performed with 4 cm⁻¹ resolutions in the range of 400–4000 cm⁻¹.

2.8 DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Differential scanning calorimetry (DSC) analysis was performed using a calorimeter (TA-60WS, Shimadzu) with a temperature range of -20 to 220 °C at a heating rate of 10 °C.min⁻¹ and atmospheric nitrogen flow rate of 50 mL.min⁻¹. Samples (approximately 3 mg) were weighed into aluminum capsules using a precision balance (± 0.0001) and an empty container was used as a reference.

2.9 VITAMIN C CONCENTRATION IN THE FILMS

The film samples (2 x 2 cm) were weighed and solubilized in 50 mL of distilled water in a shaker (TE 420 - Tecnal, Brazil) at a controlled temperature of 37 °C and 0.5 mL aliquots were withdrawn at the determined times (1, 5, 15, 30 and 60 min) for vitamin C analysis (GARCIA *et al.*, 2018a).

Ascorbic acid in ODFs was quantified using a high-performance liquid chromatography (HPLC) system composed of a quaternary pump associated with a Photodiode Array Detector (Waters 2996) and a Rheodyne model injector according the methodology described by Rosa *et al.* (2007) with modifications. A Shim-pack CLC-ODS (M) C18 analytical column (250 mm $\times$ 4.6 mm, 5.0 μ m particle size) (Shimadzu) was employed for the separation and an injection volume of 20 μ L was used. The mobile phase consisted of ultrapure water pH 2.6 acidified with metaphosphoric acid at a flow rate of 1.0 mL.min⁻¹. Detection was achieved at 244 nm (DA ROSA *et al.*, 2007). Samples were analyzed in duplicate.

2.10 STATISTICAL ANALYSIS

The mean values of the results obtained in this study were evaluated by analysis of variance (ANOVA) and Tukey's test with a confidence level of 95% using the Statistica 5.0 software (Tulsa, EUA).

3 RESULTS AND DISCUSSION

3.1 MECHANICAL CHARACTERIZATION AND BARRIER PROPERTIES OF FILMS

All formulations showed high film-forming capacity in the different concentrations of AA added, the films were homogeneous, without insoluble particles and easily removed from the plate (Figure 1).

Figure 1 - CF, F1, F2 and F3 orally disintegrating films respectively.



CF corresponds to alginate control film, F1, F2 and F3 to films added with 0.25, 0.5 and 1% of ascorbic acid, respectively.

As the concentration of AA increased, there was an increase in the thickness of the films, ranging from 0.082 to 0.107 mm (Table 1). This was expected, as with the addition of AA to the formulations there was an increase in the amount of total solids, increasing the thickness of the films. F3 and F2 differed significantly from the other formulations, similar results were observed by Pamlényi *et al.* (2022).

The mechanical properties of tensile strength and elongation showed significant differences when AA was added. The formulation with the highest addition of AA (F3) showed a 3.7% decrease in tensile strength, while elongation showed significantly higher values compared to the control film. This may be associated with the fact that AA acted, in addition to being an antioxidant, also as a plasticizer, since it had four hydroxyl groups, an ether group and a ketone, which may have interacted with the alginate matrix, thus reducing resistance traction

and increasing film elongation. These results were associated with the formation of an uncompetitive matrix, which led to greater film flexibility.

Table 1 - Thickness, mechanical characterization and barrier properties of films.

Films	CF	F1	F2	F3
Thickness (mm)	0.082±0.006 ^b	0.086±0.002 ^b	0.098±0.010 ^a	0.107±0.012 ^a
Traction (MPa)	9.51±1.01 ^a	2.64±0.40 ^b	1.85±0.46 ^b	2.46±0.59 ^b
Elongation (%)	4.63±1.24 ^c	26.78±5.97 ^b	28.43±5.68 ^b	38.84±7.38 ^a
Solubility in water (%)	100±0.000 ^a	100±0.000 ^a	100±0.000 ^a	100±0.000 ^a
WVP [g mm. (kPa day m ²) ⁻¹]	4.37±0.10 ^a	2.07±0.39 ^b	1.94±0.19 ^b	1.04±0.09 ^c
Surface pH	6.83±0.05 ^a	6.33±0.11 ^b	5.93±0.15 ^c	5.35±0.13 ^d
Disintegration time (s)	24.66±0.78 ^d	31.85±1.60 ^c	42.86±1.81 ^b	56.28±0.97 ^a

CF corresponds to the alginate control film, F1, F2 and F3 correspond to the films incorporated 0.25, 0.5 and 1% of ascorbic acid, respectively. Water vapor permeability (WVP). Equal letters in the column indicate that there is no significant difference between the means by Tukey's test ($p < 0.05$).

Pirnia *et al.* (2022) developed and characterized incense-gelatin double-layer antioxidant films enriched with ascorbic acid and *Hyssopus officinalis* essential oil. It was possible to observe that the films added with 1 and 2% of AA presented higher elongation values when compared to the control film.

Sodium alginate is hydrophilic, given this characteristic, all films studied showed 100% solubility in water. Similar results were observed by Santos *et al.* (2022) in the development of sodium alginate films with the addition of 10-40% Clitoria ternatea extract. High solubility in water is an important point when choosing the polymers used in the production of ODFs.

Water vapor permeability (WVP) measures the transfer of water vapor through the film. The films added with AA showed significantly lower values for WVP when compared to the control film. Formulations F1 and F2 did not differ from each other but differed significantly from F3 with the highest concentration of AA showing the lowest WVP. Chen *et al.* (2021) in their evaluation of sodium alginate films incorporated with thymol, found values similar to those of this work 5.2 [g mm.(kPa day m²)⁻¹] for the alginate control film and 4.3 [g mm.(kPa day m²)⁻¹] for sodium alginate films prepared with 10 mg/mL of thymol.

It is worth mentioning that there is still a great lack of information on standardized technological characteristics such as disintegration tests, mechanical properties, adequate storage conditions, packaging, and shelf life, making the characterization of ODF formulations a task that requires more studies (ADROVER *et al.*, 2015; DIXIT; PUTHLI, 2009).

3.2 DISINTEGRATION TIME

For the control film, the disintegration time was 24.66 ± 0.77 s, (Table 1) similar results were reported by Garcia *et al.* (2020) for starch films with the addition of vitamin C to the formulation of the film where the disintegration time for the starch films increased. The films added of vitamin C showed a significant increase in the disintegration time. The increase in disintegration time may be related to the thickness of the films, which, according to Table 1, was greater in the two highest concentrations of AA.

The disintegration time for F3 of 56.28 s was longer and differed significantly from F2, and F1, it was worth noting that F3 had the greatest thickness of 0.107 mm and was also the formulation with the highest concentration of ascorbic acid. All formulations differed significantly from the control however all films showed disintegration times lower than 60 s. According to Jyoti *et al.* (2011), ODFs that have a decay time below 60 s are considered as fast disintegration films.

3.3 SURFACE pH

The surface pH is an important characteristic to be evaluated in ODFs as they come into direct contact with the mouth. As the concentration of AA increased, there was a reduction in surface pH values (Table 1) when compared to the control film. With the addition of AA to the polymeric matrix, it was observed that the thickness also increased, due to the concentration of total solids in the polymeric matrix having increased, causing an increase in the disintegration time, which was influenced by the increase in thickness.

The ODFs produced had a surface pH of 6.83 for CF and 5.35 for F3, the formulation with the highest addition of AA, this decrease in pH was already expected since AA was added, which has an acidic character.

Another factor that caused this reduction is the fact that AA has a more acidic character with a pH around 4.0, which may have contributed to this significant decrease in values. Garcia *et al.* (2018) produced gelatin and starch films as vehicles for the release of vitamin C and they had surface pH values between 4.9 and 5.7.

The main functional groups present in alginate are COOH (carboxyl), OH (hydroxyl), and vitamin C COH, CO, and -O (Boonsiriwit *et al.*, 2021). These groups can form hydrogen bonds with the oral mucosa, making this oral interaction more favorable and less susceptible to irritation. Studies have reported that polymers with COOH (carboxyl), OH (hydroxyl), NH₂

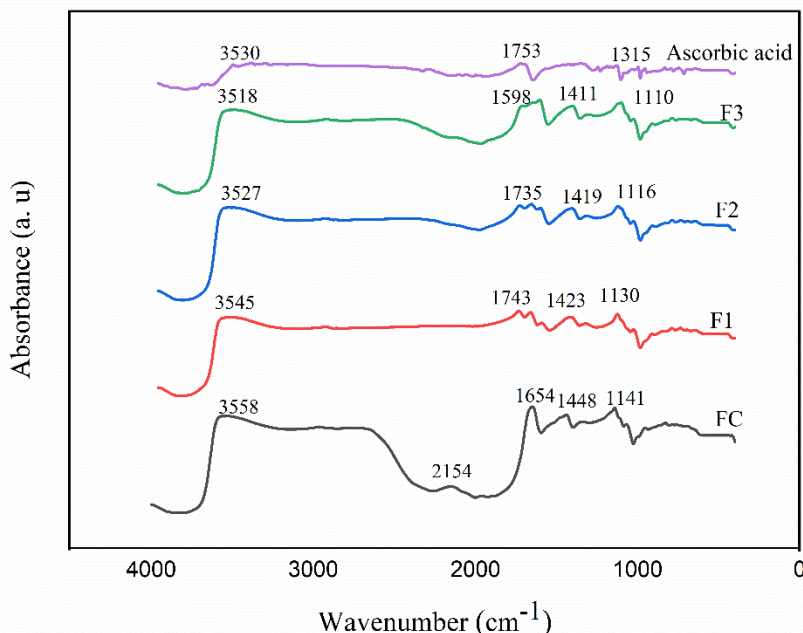
(amide), and SO_4H (sulfate groups) functional groups are more favorable for oral interactions (ANDREWS; LAVERTY; JONES, 2009).

3.4 FTIR SPECTROSCOPY MEASUREMENT

With the FTIR results (Figure 2) it was possible to observe the presence of AA in the polymeric matrix. The AA spectrum was observed at 1753 (= CO stretch), 1653 (= C-C stretch) and 1315 cm^{-1} (-CO stretch) and the bands between 3530 and 3210 cm^{-1} were assigned to free and bound -OH (VOSS et al., 2018).

The infrared spectra of the sodium alginate films showed characteristic bands at 3558 cm^{-1} (-OH), 2154 cm^{-1} ($\equiv\text{C-C}$), 1654 cm^{-1} (COO- asymmetric stretch), 1448 cm^{-1} (COO- symmetric stretch) and 1141 cm^{-1} (COC stretch) (BOONSIRIWIT et al., 2021; UMER et al., 2014). The peak at 3558 cm^{-1} can be equated to hydroxyl groups (-OH) that were compatible with the hydrophilic structure of sodium alginate as well as that of glycerol.

Figure 2 - FTIR, of alginate control films (CF), F1, F2, and F3 spectrum correspond to the films added with 0.25, 0.5, and 1% of ascorbic acid respectively. The absorption in 1743 and 1735, from 1598 cm^{-1} in F1, F2, and F3 respectively was



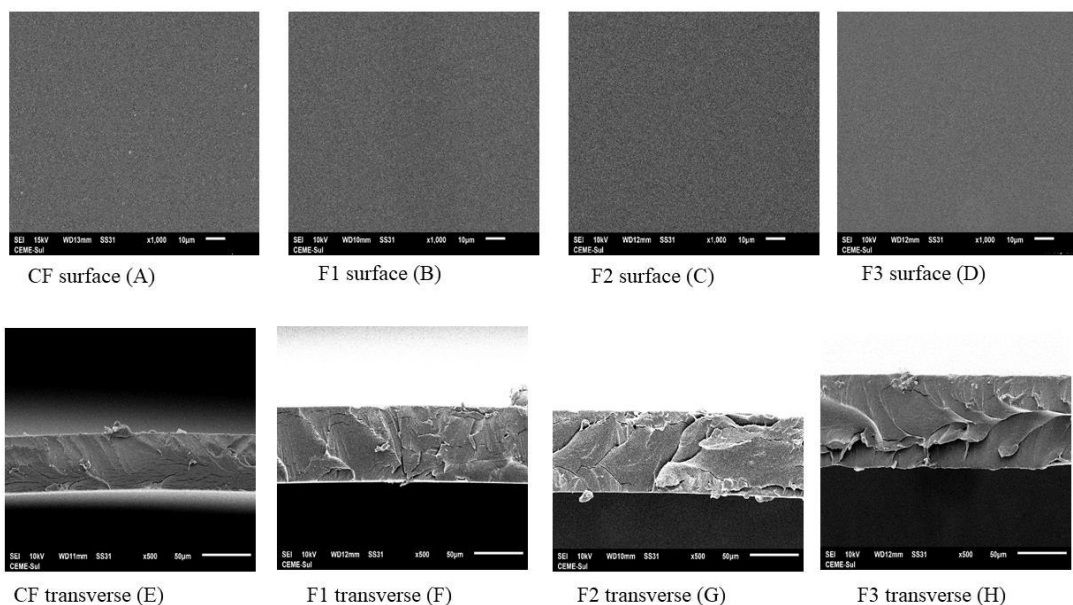
associated with the stretching of C=C and the enol-hydroxyl peak that were present in the structure of AA (DESAI; PARK, 2005; UMER *et al.*, 2014). Also, the peaks at 1423, 1419, 1411, 1130, 1116, and 1110 cm^{-1} were attributed to the stretching vibration of C=O, C=C, C=C-

OH (enol group) and C–O–C bonds present in vitamin C molecules (DESAI; PARK, 2005) which must have contributed significantly to the intensities of these bands in the FTIR spectra of the films.

3.5 SCANNING ELECTRON MICROSCOPY (SEM)

The microstructure of the films analyzed by SEM (Figure 3) showed that the surfaces of all samples did not present voids or cracks, being uniform and smooth, which indicated that the dispersion of alginate and glycerol was effective for the control film (CF), with the same characteristics observed in the incorporation of AA in formulations F1, F2 and F3. Sodium alginate films loaded with 10-40% *Clitoria ternatea* extract (CTE) were developed and characterized by Santos *et al.* (2022), and the authors observed similar results for pure alginate films, which presented a smooth surface, dense and continuous, indicating good dispersion of the alginate in the glycerol plasticizer.

Figure 3 - Surface micrographs and cryofractures of films. CF alginate control films (A, E), F1 (B, F), F2 (C, G), and F3 (D, H).



CF alginate control films and films added with 0.25, 0.5 and 1% ascorbic acid F1, F2 and F3, respectively.

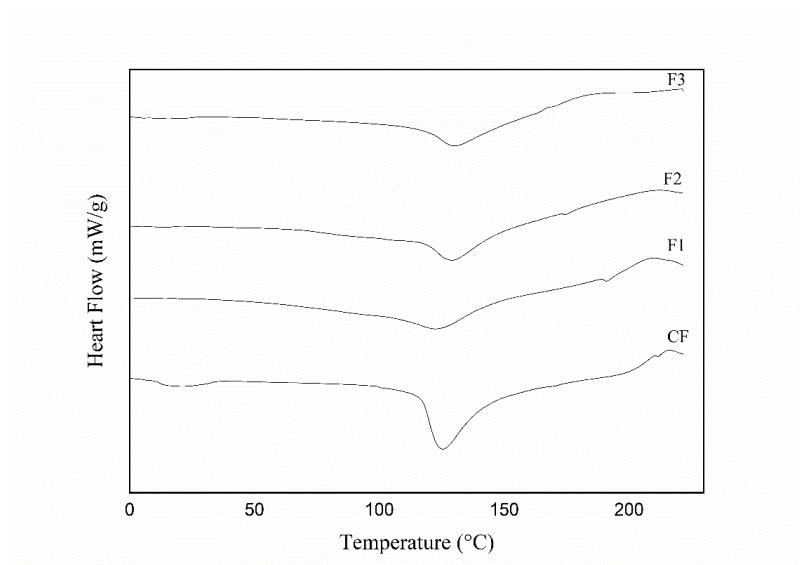
Analyzing the cross section, it was possible to observe a structure with several cracks, with discontinuous zones for the control film. The presence of these cracks in the alginate film matrix directly affected water vapor permeability, which was reduced with the addition of AA, generating a significant difference when compared to the control.

With the addition of AA F1, F2 and F3, these cracks did not decrease, the images showed that they became more compact, possibly due to the presence of OH groups between the alginate and AA. Furthermore, AA may also have acted as a plasticizer, which was suggested by observing the elongation values, which increased significantly when compared to the control. This change can be observed in fractured SEM images that showed wider and more heterogeneous cracks. Marangoni *et al.* (2022) obtained similar results in their study, they evaluated the effect of green propolis extract and silica nanoparticles (SiO_2) on the structure of sodium alginate-based films, demonstrating that the higher the SiO_2 concentration the rougher the film presented.

3.6 DIFFERENTIAL SCANNING CALORIMETRY ANALYSIS (DSC)

The thermal properties of the films were evaluated by DSC analysis (Figure 4), it is possible to observe that the melting temperature occurred at 83.03 °C, with the appearance of an endothermic peak for the control film. For films added of vitamin C, this peak occurred at 79.12, 76.52 and 72.30 °C for formulations F1, F2 and F3, respectively.

Figure 4 - DSC curves of alginate control films (CF) and films added with 0.25, 0.5 and 1% ascorbic acid F1, F2 and F3, respectively.



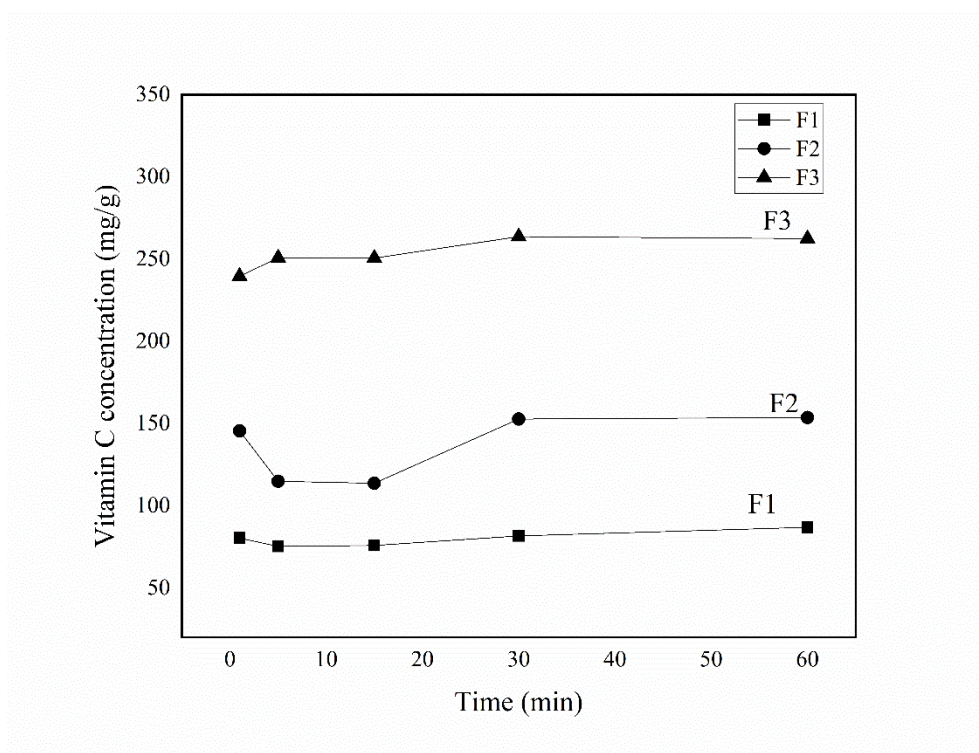
The appearance of the exothermic peak occurred at 213.40 °C for the control film. In the formulations added with AA, the exothermic peak occurred at 213.08, 209.10 and 211.75 °C for F1, F2 and F3, respectively, thus indicating the degradation of the compound. The addition of acid to the alginate matrix did not cause significant changes in the decomposition

temperature of the films, indicating good compatibility between alginate and AA. Similar results were obtained by Santos *et al.* (2022) with alginate films incorporated with different phenolic extracts.

3.7 VITAMIN C CONCENTRATION IN FILMS

The results of the vitamin C content in the films (Figure 5) showed that in 1 min of reaction, the F1 formulation presented 80.46 mg.g⁻¹ of vitamin C, releasing about 64.0% of the initial amount of incorporated vitamin C, this amount increased to 70% after 60 min. F2 the concentration of vitamin C in 1 min was 145.62 mg.g⁻¹ of vitamin C with a release of 58.2%. F3 showed 239.5 mg.g⁻¹ in 1 min with 48% of release, which increased to approximately 53% at the end of the reaction.

Figure 5 - Vitamin C concentration at different release times for formulations F1, F2 and F3.



It is possible to infer that F2 and F3 formulations can be used as daily supplements for the intake of vitamin C. According to the World Health Organization (WHO), the daily intake of vitamin C is 45 mg.day⁻¹, and the added concentrations in the orally disintegration films supply the daily dose in just one dose (film). Sodium alginate proved to be a good polymer capable of being used in the production of ODFs containing higher amounts of vitamin C, as

well as maintaining its mechanical and barrier properties, being easy to handle, and fast delivery of the compound.

Pereira *et al.* (2022) developed and evaluated cassava starch and gelatin films with added vitamin C and catuaba extract as bioactive. The authors reported that the concentration of vitamin C remained constant during the 60 min and at 5 min 97% of the initial concentration had been released. Farias *et al.* (2012) developed and evaluated cassava starch films added with acerola pulp for the vitamin C content. The authors observed that the concentration of vitamin C obtained by the films ranged from 74.13 to 3761.84 mg.g⁻¹ of film, demonstrating that these films are an additional source of this additive.

4 CONCLUSION

In this study, sodium alginate and sodium alginate and vitamin C films were visually homogeneous, without insoluble particles or defects, demonstrating high film formation capacity at different concentrations of added ascorbic acid. All formulations showed high solubility, short disintegration time, as well as a surface pH close to the buccal pH, possibly not irritating the oral mucosa. The results demonstrated that the alginate matrix can support a high concentration of vitamin C, and the F2 and F3 formulations presented concentrations above the recommended daily intake, presenting adequate mechanical and barrier properties for good handling, without losing quality, so we can state that sodium alginate can be used as a polymer for the production of orally disintegrating films, showing desirable properties for its products.

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ARTICLE III

DEVELOPMENT AND CHARACTERIZATION OF ORALLY DISINTEGRATING METHYLCELLULOSE FILMS CONTAINING VITAMIN C

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Development and characterization of orally disintegrating methylcellulose films containing
vitamin C.

Development and characterization of orally disintegrating methylcellulose films containing vitamin C

ABSTRACT

Oral disintegrating films become an option in the ingestion of active compounds due to their easy administration. The study aimed to develop and characterize orally disintegrating films (ODFs) based on methylcellulose with different concentrations of vitamin C. The films were developed by *Casting* method using the addition of ascorbic acid (0.25%, 0.5%, and 1%) beyond control and evaluated for barrier, mechanical, thermal, microstructural properties, surface pH, disintegration time, and vitamin C concentration. The increase in vitamin C concentration led to thicker films with a reduction in tensile strength of 42% and an increase in elongation of 17.09% compared to the control. The disintegration time of the films ranged from 40.89 s for the control film to 57.96 s for the formulation with 1% of vitamin C. The surface pH decreased with higher concentrations of vitamin C due to its acidic nature. Differential scanning calorimetry (DSC) indicated an increase in the melting temperature of the films with the addition of vitamin C, suggesting greater thermal stability. The stability of vitamin C in the films was evaluated by High-performance liquid chromatography (HPLC) showing a reduction of 60 % for the formulation with 0.25% ascorbic acid in 56 days of storage, while for the formulation with 1% vitamin C the reduction was 70% in 56 days of storage. The study demonstrated that methylcellulose can be used as a polymer for ODFs and that even at lower concentrations of ascorbic acid it presented adequate properties and a controlled release of the active compound.

Keywords: Methylcellulose; Oral films; Thermal analysis; High-performance liquid chromatography; Ascorbic acid.

1 INTRODUCTION

Oral disintegration films (ODFs) have been widely used as vehicles for administering active compounds orally, due to their prompt disintegration in the oral cavity. Its notable features are ease of administration, greater surface area, no need to consume water for ingestion, and recommendations for pediatric and geriatric patients, and dysphagic people (GARCIA *et al.*, 2020a; GUPTA; KUMAR, 2020). ODFs can be produced from the combination of one or more polymers, forming a thin film capable of incorporating the active compound of interest (CILURZO *et al.*, 2018; PALEZI *et al.*, 2023).

The selected polymer must be water-soluble, non-toxic, could not cause irritation, have good spreadability, mechanical properties, and be compatible with the active compound (LEE *et al.*, 2017). Among the numerous polymers available, methylcellulose stands out.

Methylcellulose (MC) is an example of a biodegradable polymer that has been used in the manufacture of films due to its good film-forming properties in addition to its ability to serve as a reinforcing material to improve mechanical properties (DING; ZHANG; LI, 2015b). Studies show that this polymer, in addition to providing good barrier protection, is also used in tablet and capsule formulations as it helps in the containment and release mechanisms for active compounds (BEAULIEU *et al.*, 2009).

Polymers originated from cellulose such as MC are known for their solubility in water, making them suitable for a variety of applications, resulting in transparent, economically advantageous, shiny, oil-resistant, but water-sensitive films (BIRON, 2017). MC is a cellulose derivative with minimal modifications, the methoxy groups replace hydroxyl groups, making it less hydrophilic (TURHAN; ŞAHBAZ, 2004). This makes it a widely used component in solid pharmaceutical product formulations, acting as a binder, coating agent, and disintegrant in tablets, as well as in matrix tablets to achieve the controlled release of active substances (BRADY *et al.*, 2017).

Vitamin C is water-soluble, being a set of organic molecules essential for supporting metabolism, energy production, and cell reproduction (ABD EL AZIM *et al.*, 2015). Furthermore, it plays a significant role in preventing various health problems, such as cancer, cataracts, heart disease, among others, and its deficiency is associated with the condition known as scurvy (PADAYATTY *et al.*, 2003).

The human body is unable to produce and store vitamin C, making regular intake of adequate amounts essential, whether through food or supplements, the objective of this research was to develop an ODF using MC as a polymer added with different concentrations of acid ascorbic as an alternative to vitamin C supplementation.

2 MATERIAL AND METHODS

2.1 MATERIAL

Methylcellulose (99%) was provided by the company Colorcon do Brasil Ltda (Cotia, SP, Brazil), the glycerol was purchased from Êxodo Científica (Sumaré, Brazil), the food grade artificial coloring (green) was purchased from local stores. Vitamin C (99%) was purchased from Sigma-Aldrich (São Paulo, Brazil). All the chemical reagents used were of analytical grade.

2.2 FILM PRODUCTION

The films were prepared using the casting method, following the methodology described by Filipini *et al.* (2020) with adaptations. The MC films were obtained by dispersing 1% (m/v) of methylcellulose in water and glycerol in a proportion of 10% over the mass of the biopolymer in a thermostatic bath. In the first stage, homogenization was carried out at 25 °C for 30 min and in the second stage the temperature was raised to 50 °C for more 30 min. The solution was cooled to 30 °C and concentrations of 0.25, 0.5, and 1% (m/v) of ascorbic acid were added. These concentrations were obtained through preliminary tests. 20 g of the film formulations were poured into Petri dishes ($\varnothing = 9$ cm) and dried at 35 °C for 12 h in an air circulation oven (Q316M – Quimis, Brazil). The dried films remained for 24 h in desiccators at 50% relative humidity (RH) before being analyzed. A control film was developed without the addition of ascorbic acid. The control film and the films added with 0.25, 0.5 and 1% ascorbic acid were named CF, F1, F2, and F3, respectively (Table 1). Green food coloring was added to all formulations for better visualization of the films, since MC is extremely transparent, 1 drop (0.05 mL) of the coloring was added immediately after homogenization with glycerol.

Table 1 - Coding and produced ODFs.

Codification	Concentration of compounds (%)		
	Methylcellulose (m/v)	Glycerol (m/v)	Ascorbic acid (m/v)
CF	1.0	10	-
F1	1.0	10	0.25
F2	1.0	10	0.5
F3	1.0	10	1.0

CF, F1, F2 and F3 correspond to the control methylcellulose film and the films added with 0.25, 0.5 and 1% ascorbic acid, respectively.

2.3 CHARACTERIZATION OF THE MECHANICAL AND BARRIER PROPERTIES OF THE FILMS

The thickness was measured in ten random positions of the film with a digital micrometer (IP54 – Insize, Brazil). The mechanical properties of tensile strength (MPa) and elongation at break (%) were determined with a texture analyzer (TA.Xtplus – Stable Micro

Systems, England) according to D-882-02 standard method (ASTM, 2013). The films were cut into strips (50 × 25 mm) to be analyzed and the test was carried out with an initial separation of the grips of 50 mm and a crosshead speed of 1 mm.s⁻¹. The analysis was carried out with ten replicates.

The fold endurance of ODFs was measured by bending the film in place until it broke (CAROLINA VISSER *et al.*, 2017b). For this purpose, three ODFs samples were tested, and the number of bends was recorded as the fold endurance value.

Water vapor permeability (WVP) was evaluated according to E96-00 standard method (ASTM, 2013). Briefly, plastic bottles were filled with 15 g of silica gel and sealed with films. The permeation cell was placed in a desiccator at 25 °C and 75% of RH. The vials were weighed every 24 h for 7 days and WVP was determined as described in Equation 1, W, L, A, t and ΔP is the silica mass gain (g), film thickness (mm), permeation area (m²), time of mass gain (day) and vapor pressure difference across of the film (kPa), respectively.

$$\text{WVP (g mm kPa}^{-1} \text{ day m}^{-2}) = \frac{W \cdot L}{A \cdot t \cdot \Delta P} \quad (1)$$

Water solubility (%) was determined by gravimetry as described by Gontard *et al.* (1994). The films were placed in an aluminum capsule, dried at 105 °C in an oven (A15-E – DeLeo, Brazil) to determine the weight of the initial dry film (wi), then it was submerged in 50 mL of distilled water and shaken at 150 rpm for 24 h on an orbital shaker (TE 420 - Tecnal, Brazil). The insoluble materials were dried at 105 °C for 24 h and the weight of the final dry films (wf) was determined. Water solubility was calculated as the ratio between wi and wf.

2.4 SURFACE pH

The surface pH was evaluated according to Prabhu *et al.*, (2011) using phosphate buffer pH 6.8, to simulate saliva, prepared according to Wong; Yuen; Peh, (1999). Strips of ODFs (3 cm x 2 cm) were placed in contact for 30 s with 0.5 mL of buffer solution and after 1 min the pH was determined using a benchtop pH meter (Q400AS). Samples were analyzed in triplicate.

2.5 DISINTEGRATION TIME

The disintegration time was determined according to the method described by Perumal *et al.* (2008) where film samples (3 x 2 cm) were diluted in 50 mL of phosphate buffer solution (pH 6.8) under agitation at 100 rpm.min⁻¹ at 37 °C on an orbital shaker (TE 420 - Tecnal, Brazil). Disintegration time was determined as the time required (min) for the sample to completely dissolve. Analyses were performed in triplicate.

2.6 SCANNING ELECTRON MICROSCOPY (SEM)

The surface and cross-section images of the films were obtained by a microscope (JSM-6610LV, Jeol), operating at 15 kV. The films were fixed on aluminum stubs, coated with gold, and the images were obtained in 3000x magnification of the surface and 1000x on the cross section.

2.7 FOURIER TRANSFORM-INFRARED SPECTROSCOPY (FTIR)

Functional groups present in the films were determined in spectra obtained by Fourier transform infrared spectroscopy (FT-IR) in the range of 400–4000 cm⁻¹ in an FT-IR equipment (IRPrestige-21, Shimadzu).

2.8 DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Differential scanning calorimetry (DSC) analysis was performed using a calorimeter (TA-60WS, Shimadzu) with a temperature range from -20 to 300 °C, at a heating rate of 10 °C.min⁻¹ and an atmospheric nitrogen flow rate of 50 mL.min⁻¹.

2.9 ASSESSMENT OF THE STABILITY OF VITAMIN C IN FILMS DURING THE STORAGE PERIOD

The film samples were stored under controlled temperature conditions at 30°C and protected from light for a period of 56 days. Every 7 days, film samples (2x2 cm) were weighed and solubilized in 50 mL of distilled water and incubated at 37°C on a shaker for 60 min to verify the ascorbic acid concentration. During the incubation time, aliquots were removed at specific times (1, 5, 15, 30 and 60 min) (GARCIA *et al.*, 2018b).

Ascorbic acid was analyzed by high-performance liquid chromatography (HPLC). Aliquots of 20 μL of sample solution were injected into a C18 column (Zorbax, Eclipse XDB) (4.6 x 150 mm, 5 μM) and their absorbance at 244 nm was monitored according to the methodology described by Rosa *et al.* (2007) with modifications. The column was eluted at a flow rate of 1.0 mL min^{-1} with ultrapure water pH 2.6 acidified with metaphosphoric acid. Samples were analyzed in duplicate.

2.10 STATISTICAL ANALYSIS

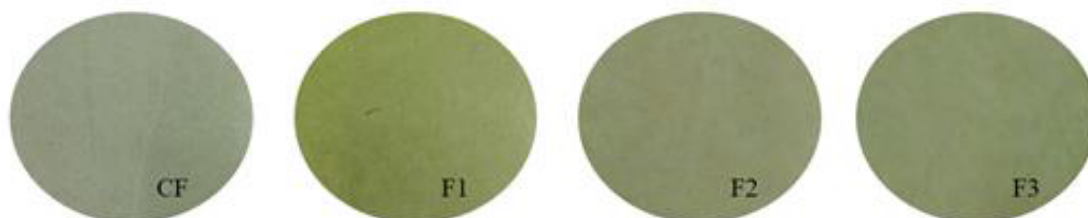
All analyzes were performed in triplicate and the results presented as mean $\pm$ standard deviation. Analysis of variance (ANOVA) and Tukey test ($p < 0.05$) were performed to compare the mean among three assays. Data were evaluated using the Statistic program (version 5.0, StatSoft, Inc., Tulsa, USA).

3 RESULTS AND DISCUSSION

3.1 MECHANICAL AND BARRIER PROPERTIES OF FILMS

The films were homogeneous, without insoluble particles or defects, and it was easy to remove from the petri dish, these characteristics could be related to the easy solubilization of vitamin C in the film-forming solution (Figure 1). All formulations evaluated demonstrated high film-forming capacity.

Figure 1. Visual aspect of orally disintegrating films CF, F1, F2 and F3.



CF corresponds to the methylcellulose control film, F1, F2, and F3 to the films added with 0.25, 0.5, and 1% ascorbic acid, respectively.

Table 2 presents the characteristics of the films produced. The thickness of the films increased with the increase in the concentration of vitamin C added to the films, varying from 0.0363 to 0.0687 mm (Table 2), which is expected, as the increase in the concentration of vitamin C increases the amount of total solids, which causes an increase in film thickness, even so, the films are within the rapid dissolution classification according to Jyoti *et al.* (2011).

Table 2. Thickness, mechanical, barrier, surface pH and film disintegration time properties.

Films	CF	F1	F2	F3
Thickness (mm)	0.036 ± 0.004^c	0.046 ± 0.007^b	0.040 ± 0.004^{bc}	0.068 ± 0.008^a
Tensile strength (MPa)	27.74 ± 6.50^a	20.54 ± 1.52^{bc}	21.67 ± 1.79^b	16.07 ± 1.53^c
Elongation at break (%)	28.76 ± 4.73^a	30.83 ± 3.92^a	32.12 ± 7.74^a	33.68 ± 1.14^a
Fold endurance	>300	>300	>300	>300
Water solubility (%)	100	100	100	100
WVP [g.mm.(kPa.day.m ²) ⁻¹]	4.33 ± 0.11^a	3.87 ± 0.25^{ab}	2.82 ± 0.51^b	3.59 ± 0.51^{ab}
Surface pH	6.80 ± 0.10^a	6.30 ± 0.11^b	5.73 ± 0.08^c	5.35 ± 0.13^d
Disintegration time (s)	40.89 ± 0.31^d	50.42 ± 0.20^c	55.67 ± 0.32^b	57.96 ± 0.60^a

CF, F1, F2, and F3 correspond to the control methylcellulose film and the films added with 0.25, 0.5 and 1% vitamin C, respectively. Water vapor permeability (WVP). Means with different subscripts on the same line indicate significant differences ($p < 0.05$).

The evaluation of the tensile strength of the films demonstrated that the control film (CF) differed significantly ($p < 0.05$) from the formulations added with vitamin. The addition of vitamin C reduced the tensile strength, and the formulation with the highest concentration (F3) showed a lower tensile strength value. Filipini *et al.* (2020) produced methylcellulose films added with jambolão extract (*Syzygium Cumini*) and obtained tensile strength values of 16.1 MPa for the methylcellulose control film.

In the study realized by Kowalczyk *et al.* (2021) edible films of corn starch and methylcellulose incorporated with fireweed extract (*Chamaenerion angustifolium L*) were developed, the authors report that the tensile strength for methylcellulose films was approximately 26 MPa, due to its more crystalline structure.

The influence of vitamin C concentration on the stretching property was not significant. The values increased as the concentration increased, but not to the point of significantly influencing this property.

The films presented values above 300 folds for the Folding hardness test. The greater the folding endurance, the lower the chance of the film breaking during removal from the packaging and administration. Barbieri (2023) found similar results in his research with starch/gelatin films, which at all concentrations tested showed resistance to folding above 300 times.

All films demonstrated complete solubility in water due to the high hydrophilic nature of methylcellulose. This phenomenon is due to the great affinity of the polymer with water, as well as the polarity of the solvent. The capacity for high solubility in water is a relevant attribute for the application of polymers in the manufacture of controlled-release products for active compounds (YU *et al.*, 2015).

The incorporation of different concentrations of vitamin C in the films resulted in a decrease in WVP water vapor permeability, with F2 differing statically from the control methylcellulose (CF) film. Similar results were found by Filipini *et al.* (2020) when characterizing methylcellulose films with the addition of jambolão extract. The reduction in WVP in films with vitamin C may be related to crystallinity, molecular orientation and the affinity between the polymer and the active compound.

3.2 SURFACE pH

The oral mucosa has a high vascularization, which facilitates the absorption of active compounds. For the active compound to be absorbed efficiently, the pH of the film must be compatible with the natural pH of the oral mucosa (generally between 6.5 and 7.5, with some variations possible). Many compounds are sensitive to pH, which is an essential parameter for maintaining the chemical stability of the compound until its release. Higher concentrations of vitamin C in the formulation resulted in a reduction in the pH values of the surface, which was expected since ascorbic acid has an acidic pH, as can be seen in Table 2, in comparison with the control film.

As film thickness increased, surface pH values decreased while films with greater thickness and lower surface pH showed longer disintegration times. Shin and Han (2024) observed similar results in the study where they developed ODF of hyaluronic acid with concentrations of vitamin C. The highest concentrations of vitamin C showed surface pH values between 3.6 and 3.9.

3.3 DISINTEGRATION TIME

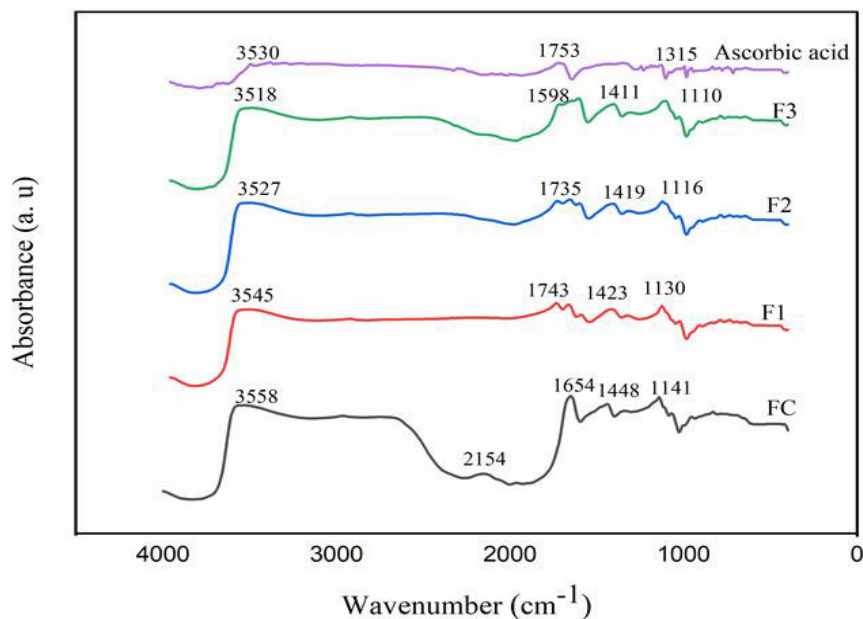
To be considered a viable ODF, it must be able to disintegrate quickly and efficiently in contact with water (SAPIEE *et al.*, 2023). The results in Table 2 demonstrate that the control film (CF) had a disintegration time of 40.89 ± 0.31 s. However, when adding vitamin C to the formulation, a significant increase in disintegration time was observed as the concentration of vitamin C increased. This increase in disintegration time can be attributed to the thickness of the films, which was more pronounced in the two highest concentrations of vitamin C (F2 and F3). All formulations remained with a disintegration time below 60 s, and it is very important because to be considered a flash release films, it needs to be completely disintegrate in 60 s.

Kowalczyk *et al.* (2021a) evaluated the effects of increasing concentrations (0, 0.0125, 0.025, and 0.05% w/w) of freeze-dried fireweed aqueous extract (FE) on the release and antioxidant properties of edible films based on corn starch and methylcellulose. The authors observed that the methylcellulose films were rapidly dissolved in water and ensured a more complete and multi-mechanistic FE release than the corn starch-based film.

3.4 FOURIER TRANSFORM-INFRARED SPECTROSCOPY (FTIR)

FTIR spectroscopy was performed to investigate the interactions between MC and vitamin C in films (Figure 2). In the spectrum of the MC film, peaks are observed at 3525 cm^{-1} (associated with the stretching vibration of the hydroxyl group (O–H)), 2943 cm^{-1} (corresponding to the asymmetric stretching vibration of C–H), 1463 and 1371 cm^{-1} (related to the in-plane strain vibration of δ (C–H)), 1174 cm^{-1} (attributed to the C–O–C stretching mode from glycosidic units) and 943 cm^{-1} (related to OCH_3 groups).

Figure 2. FTIR spectrum. CF, Vit C, F1, F2, and F3 correspond to the control methylcellulose film, vitamin C, and the films added with 0.25, 0.5, and 1% vitamin C respectively.



The absorption in 1770, 1768 and 1782 cm^{-1} observed in F1, F2, and F3 respectively is associated with the stretching of the C=C bonds and the enol-hydroxyl peak, characteristics present in the structure of ascorbic acid. Furthermore, the peaks at 1467, 1454, 1394, 1172, 1174, and 1172 cm^{-1} are related to the stretching vibration of C=O, C=C, C=C–OH (enol group) bonds as well as C–bonds, O–C present in vitamin C molecules (DESAI; PARK, 2005). These characteristics contributed significantly to the intensities of the bands observed in the FTIR spectra of the films.

Another characteristic of the spectra are the peaks that appear in the range from 1467 cm^{-1} to 1782 cm^{-1} , which can be attributed to the deformations of the carboxylate groups (COO^-) in the methylcellulose film matrix. The control film and the formulations containing vitamin C exhibit shifts and intensity variations of these peaks in this region, indicating a possible interaction between the film matrix and vitamin C.

3.5 DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The thermal properties of the films were evaluated by DSC analysis to determine the glass transition (T_g) and melting temperature (T_m) and the data are shown in Table 3.

Table 3 - Thermal properties of the films obtained by differential scanning calorimetry (DSC).

Formulations	T_g ($^{\circ}\text{C}$)	T_m ($^{\circ}\text{C}$)
Vitamin C	-	197.74
CF	77.24	116.10

F1	109.18	168.79
F2	87.56	171.81
F3	91.36	176.48

CF, F1, F2, and F3 correspond to the control methylcellulose film and the films added with 0.25, 0.5 and 1% vitamin C, respectively. Tg: glass transition; Tm: melting temperature.

Vitamin C has a melting temperature of around 197.74 °C, the control film had a melting temperature of 116.10 °C and for formulations with the addition of ascorbic acid the melting temperature was at higher temperatures.

The results show that the addition of vitamin C to the films increased its melting temperature (Tm) when compared to the control film. This increase in Tm suggests that the presence of ascorbic acid is affecting the intermolecular forces and molecular structure of the films, leading to a change in thermal properties. Higher Tm indicates more thermally stable films.

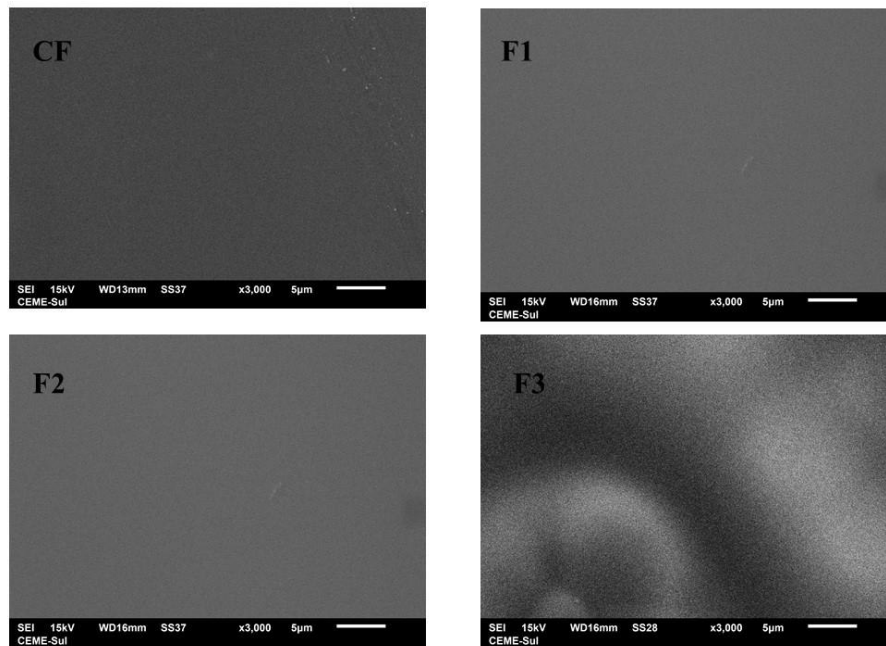
Palezi *et al.* (2023) produced oral disintegration films based on sodium alginate with the addition of 0.25%, 0.5% and 1% vitamin C where the endothermic peak for films with added vitamin C occurred at 110, 39°C, 114.62°C and 115.24°C, respectively.

Filipini *et al.* (2020) produced methylcellulose films incorporated with jambolão extract in concentrations of 10, 30 and 50%. The authors observed that the films presented a Tm of 174.37 °C for the control film and the films with jambolão extract the Tm was 178.06, 176.46, and 161.46 °C respectively.

3.6 SCANNING ELECTRON MICROSCOPY (SEM)

The microstructures of the surfaces and cross-sections of the films were examined using a scanning electron microscope (Figures 3 and 4). Analyzing the surface of the films (Figure 3), was possible to observe that all formulations exhibited a surface free of insoluble particles or bubbles, suggesting a good dispersion of methylcellulose and glycerol in the control film (CF), as well as in formulations with the addition of vitamin C. However, formulation F3 showed noticeable differences, indicating an unequal concentration of ascorbic acid in different regions of the film. This behavior may be the result of the migration of lower density compounds to the film surface during the drying process.

Figure 3 - Scanning electron microscopy of the surface of methylcellulose films.



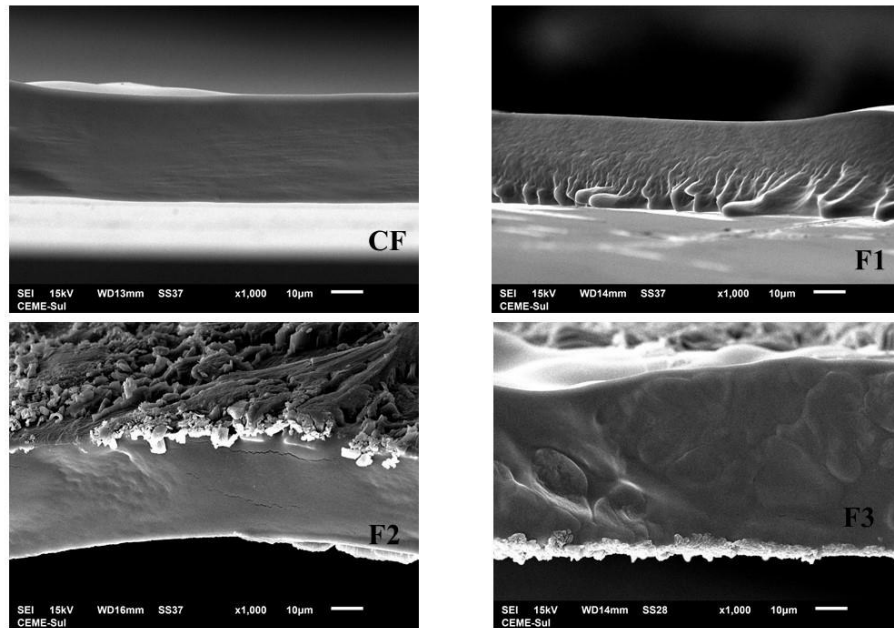
CF, F1, F2, and F3 correspond to the methylcellulose control film and the films added with 0.25, 0.5, and 1% vitamin C, respectively.

Figure 4 shows images referring to the transversal structure of the films, it is possible to observe that the film composed only of methylcellulose had a compact structure and was free of grooves, pores or insoluble particles. However, in formulations F1, F2, and F3, layers and grooves were observed in the transverse structure, resulting from the addition of vitamin C. This behavior may be attributed to the interaction of groups (-OH) between methylcellulose and ascorbic acid, influencing the organization of molecular chains when ascorbic acid is added, leading to this heterogeneity and the formation of discontinuous areas.

Filipini *et al.* (2020) observed similar results for methylcellulose films with jambolão extracts. The authors observed that when 30 and 50% of jambolão extract were added, there were changes in the film matrix caused by the interaction of the polymeric network with the compounds present in the extract.

Figure 4 - Scanning electron microscopy of the cross-section of methylcellulose films.

CF, F1, F2, and F3 correspond to the methylcellulose control film and the films added with 0.25, 0.5,



and 1% vitamin C, respectively.

3.7 ASSESSMENT OF THE STABILITY OF VITAMIN C IN FILMS DURING THE STORAGE PERIOD

The films were analyzed observing the stability of vitamin C during the storage period, and the results can be observed in Figure 5, 6 and 7. It is worth mentioning that according to the World Health Organization (WHO), the daily intake of vitamin C is $45 \text{ mg} \cdot \text{day}^{-1}$, therefore the concentrations added to the oral disintegration films supply the daily dose in just one film.

Figure 5 - Stability of vitamin C as a function of storage (days) at different release times. A corresponds to F1 (0.25% vitamin C).

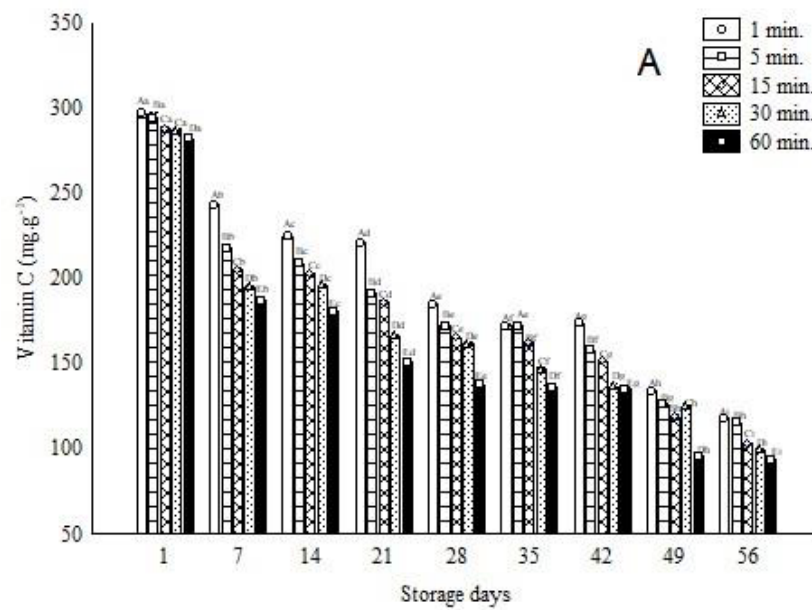


Figure 6 - Stability of vitamin C as a function of storage (days) at different release times. A corresponds to F2 (0.5% vitamin C).

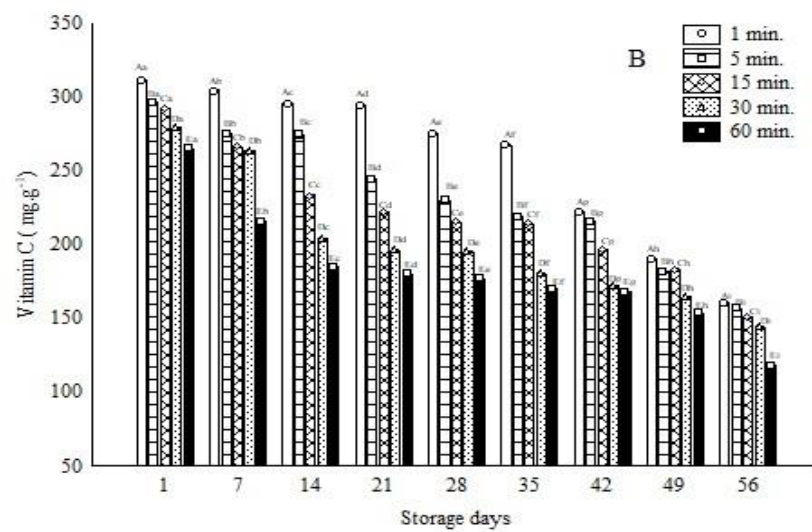


Figure 7 - Stability of vitamin C as a function of storage (days) at different release times. A corresponds to F3 (1% vitamin C).

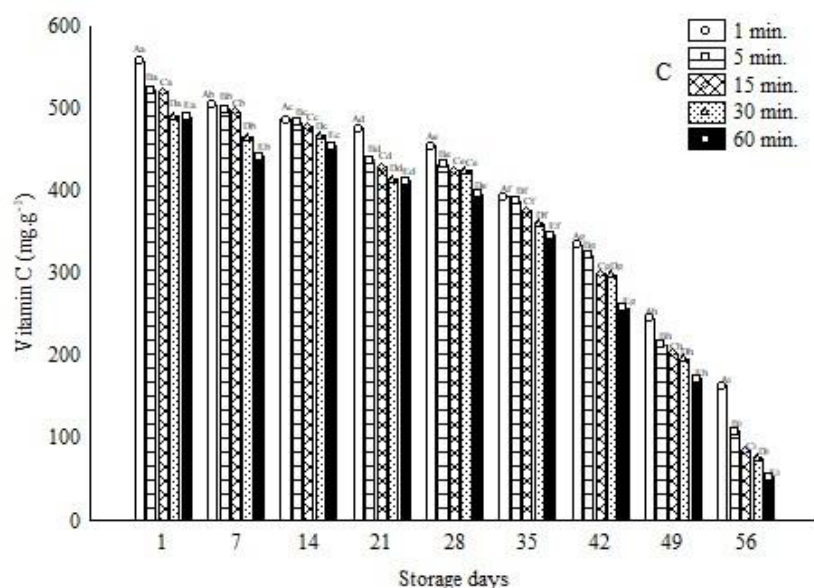


Figure 5 shows that for F1, in 1 min of reaction, on the first day of storage, the concentration of vitamin C obtained was 296.27 mg.g⁻¹, releasing around 70% of the initial content added, and after 60 min of reaction the concentration decreased to 281.19 mg.g⁻¹. The concentration after 56 days of storage decreased to 117.56 mg.g⁻¹, which was affected by the degradation of ascorbic acid and had a release of 47% from the initial value.

The F2 formulation (Figure 6) presented 310.32 mg.g⁻¹ of vitamin in 1 min of reaction, on the first day of storage, and was reduced to 264.61 mg.g⁻¹ at the end of 60 min of reaction, resulting in 100% release of vitamin C. After 56 days of storage, F2 showed a concentration of 159.25 mg.g⁻¹ in 1 min of reaction and was reduced to 117.18 mg.g⁻¹ after 60 min, demonstrating the degradation of vitamin C throughout the storage period.

The results show that for formulation F3 (Figure 7) the concentration on the first day of analysis in 1 min was 556.53 mg.g⁻¹ and at the end of 60 min the concentration presented was 488.57 mg.g⁻¹ with a release percentage of 97.71%. At the end of the storage period (56 days), a concentration of 163.8 mg.g⁻¹ was obtained, showing a significant loss over the days, demonstrating a reduced stability of vitamin C depending on the storage time.

The films with added vitamin C presented values above those recommended for RDI (Recommended Daily Intake), the losses of vitamin C during the storage period demonstrate the already expected behavior of vitamin C, since this is a very unstable molecule when exposed. to air, light, heat, humidity, oxygen, it decomposes into biologically inactive compounds.

Palezi *et al.* (2023), in the study of an oral disintegration film added with vitamin C, observed values of 145.62 mg.g⁻¹ and 239.5 mg.g⁻¹ respectively for the formulations added with 0.5 and 1% vitamin C. Demonstrating that the alginate matrix was capable of forming a concise film containing vitamin C and with concentrations within those recommended for RDI (Recommended Daily Intake).

4 CONCLUSION

In the present study, films made with methylcellulose, methylcellulose and vitamin C were visually homogeneous, without insoluble particles or defects, demonstrating high filmogenic capacity at different concentrations of added vitamin C. All formulations showed high solubility, short disintegration time and surface pH close to the oral pH, possibly not irritating the oral mucosa. The results demonstrate that the methylcellulose matrix can withstanding a high concentration of vitamin C, presenting adequate mechanical and barrier properties for good handling without loss of quality. In addition to release the compound effectively, it can be used as a polymer for the production of orally disintegrating films presenting desirable properties. Formulation F2 proved to be more stable during the days of storage, however the three formulations showed the capacity to be used as vehicles for vitamin C supplementation, they can be used according to the purpose and need to be used.

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CHAPTER IV

General Conclusion

Oral disintegrating films were produced and it represents an important innovation in the administration of active compounds, providing greater comfort as well as greater adherence to treatment, especially in people with difficulty of swallowing (dysphagia), pediatric and geriatric populations, as well as others who face challenges with traditional products such as capsules and tablets.

The polymers, sodium alginate and methylcellulose, proved to be good polymeric matrices for the development of orally disintegrating films. The matrices were soluble and had a short disintegration time when hydrated. In general, they showed high film-forming capacity and good incorporation of the vitamin C. The films had a pH within a range that does not harm the oral mucosa beyond its thin thickness.

Vitamin C was able to be incorporated into the matrices and when hydrated it was released, presenting a good available concentration of the compound. The study contributed significantly to new applications of the studied polymers, which also showed promise for the production of ODFs. Furthermore, they can be a basis for studies with other active compounds, in addition to improve the application of the vitamins, they represent a modern and convenient approach to the supplementation of compounds, looking for to meet the needs and facilitating adherence to vitamin C supplementation.

CHAPTER V

Waste generated and destination

All chemical waste generated during the development of this study was stored, identified, and discarded following the waste management plan of the School of Chemistry and Food (EQA) and the protocols of the Laboratory of Food Technology (LTA) - FURG.

SUGGESTION FOR FUTURE STUDIES

- Evaluate new polymers by applying vitamin C and checking their behavior during the storage period.
- Add flavorings to polymeric matrices.
- Carry out sensory analysis to check the acceptance of the films.
- Use other active compounds in polymeric matrices, checking the release behavior of the compound.

CHAPTER VI

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