Development of Orodispersible Films for the Release of Drugs in Elderly Patients

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Abstract

The interest of consumers for natural products with functional appeal is growing. Due to the low cost of production, non-toxic, from a renewable source, starch is a promising raw material for the production of biodegradable membranes (films). However, the high hydrophilicity of the starch-based membranes represents a serious technological limitation to their commercialization, since the properties of the membranes are affected by the variation of the relative humidity of the air during its storage or its use. This work aims at the production and characterization of oral starch and starch films associated with Chondroitin Sulfate (CS) for the release of chlorhexidine for elderly patients. Six film formulations were produced by casting with 4% starch and sorbitol as plasticizer at 20% and 50% concentrations for F1 and F2, films containing 5% starch and 50% sorbitol (F3), and films with starch and chondroitin in the proportions 90:10, 85:15 and 80:20 for the total 5% polymer solution and 50% sorbitol as plasticizer for F4, F5 and F6. The films were characterized by macroscopic analysis, weight uniformity, flexibility, surface pH, disintegration test and swelling. The results indicated that changes in transparency, disintegration time and degree (%) of swelling were dependent on the concentration of chondroitin sulfate. The increase in CS concentration decreased the hydrophilicity of the starch. The plasticizing effect of sorbitol can also be demonstrated by the increased flexibility of the films. The F5 and F6 formulations developed with the unprecedented polymeric association of starch and chondroitin sulphate showed satisfactory morphological characteristics, swelling and disintegration levels, and were selected for new production plus 0.12% chlorhexidine. Both formulations were homogeneous with respect to the drug content, and F6 released the chlorhexidine in a more controlled way than the F5, concluding that films with starch and CS in the proportion of 80:20 in 5% of polymer solution is ideal to be used as a novel drug controlled release matrix.

Key Words: Chlorhexidine, Controlled drug release, Saliva

Introduction

The society's and health professionals' search for healthier and lower environmental impact products has grown widely in the last decades. Due to this behavioral change of the consumer, the industries are induced to increasingly seek products with a sustainable character and often with functional appeal [1].

Polymers from renewable natural sources have been a focus of interest for the development of new technologies aimed at environmental preservation and the search for potential substitution alternatives for conventional plastics from petroleum. In this context, starch has been considered a polymer with high potential to produce biofilms, being low cost, high availability, renewable and biodegradable. However, a number of limitations are observed in relation to their hydrophilic characteristics and water vapor permeability [2]. One of the alternatives to decrease the hydrophilic characteristics of the starch is the association of these with other polymers or other substances that allow the production of more resistant films.

These films or membranes based on natural polymers have gained prominence in the food industry, due their potential for use as edible packaging [3,4]; but also in the pharmaceutical industry, used to manufacture polymer coatings for modified release systems [5]; and also in the production of films of oral degradation [1]. This fact encourages the production of a promising polymer matrix for use in both fields, with specific modifications for each use.

Chondroitin sulfate is a natural, non-toxic polymer with mucoadhesive properties and is one of the structural components of great importance present in connective tissues of animals mainly in cartilage. It is composed of D-glucuronic acid bound to N-acetyl-Dgalactosamide [5].

Chlorhexidine corresponds to a broad spectrum antimicrobial and its formula consists of two symmetrical rings of 4-chlorophenyl and two groups of biguanide connected by a central chain of hexamethylene. Chlorhexidine gluconate is a chemical antiseptic, antifungal and bactericidal compound capable of eliminating both gram-positive and gram-negative microorganisms, but it is less efficient against gram-negative microorganisms.

Also, being a bacteriostatic in low concentrations, preventing the proliferation of bacteria. Chlorhexidine has a high affinity for bacteria, probably due to adsorption of the cationic molecule (positive) to the anionic (negative) cell wall of the microorganism. This adsorption increases the permeability of the bacterial membrane, opening true craters, allowing the penetration of chlorhexidine in the cytoplasm, causing the death of the bacteria [6-8].

In addition, it presents as an antimicrobial agent that presents high substantivity, that is, high maintenance capacity for a long time in the oral cavity, showing properties of adsorption on the dental surface, and presenting an action against Streptococcus mutans, mainly for its capacity of to adhere to extracellular polysaccharides [6-8].

This study aims the development of orodispersible starch films and the association of starch with chondroitin sulfate with controlled hydrophilic characteristics for the release of chlorhexidine in elderly patients.

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Materials and Methods

Materials

For the production of the membranes (films) corn starch (VIAFARMA®) and Chondroitin Sulphate (FAGROM®) were used as polymers; sorbitol (VIAFARMA®) as plasticizer, Chlorhexidine Gluconate (MAPRIC) as active and distilled water as solvent.

Film development

Six formulations were developed (*Table 1*). Formulations F1 and F2 were produced with 4% starch solution and sorbitol in the proportion of 20 and 50%, respectively. For F3, F4, F5 and F6, 5% of polymer solution and 50% of sorbitol were used as plasticizers. F3 was formulated with 100% starch while F4, F5 and F6 were formulated with starch and CS in proportions of 90:10; 85:15 and 80:20, respectively.

Table 1. Produced films' composition.

Formulations	Starch (%)	CS (%)	Sorbitol (%)
F1	4	0	20
F2	4	0	50
F3	5	0	50
F4	90*	10*	50
F5	85*	15*	50
F6	80*	20*	50
*Percentage of starch and CS for each 5 g of polymer/100 g of the film-forming solution			

The dental films were prepared by the casting method. The sorbitol was added to the water, then the starch was sprayed into the water, with constant stirring to a temperature of 90 to 95, maintaining that temperature for 10 minutes to establish the intermolecular bonds and, thus, to favor gel formation. For starch and CS membranes, sorbitol was added to the water and, under constant stirring and heating at about 45°C, CS was added. After 10 minutes, the starch was added and the temperature was raised to that necessary to form the film-forming solution. At the end of the process, the solution was individually distributed by weight in an acrylic plate with marked spaces for each film (approximately 14 × 2 cm) and stored in an oven (LABTRADE® MOD. EB100) at 37 ºC (± 2 ºC) for a period of 24 hours.

Characterization of the Starch and Starch Films with Chondroitin Sulfate

Macroscopic evaluation

The films were evaluated macroscopically for the parameters of presence of bubbles, transparency, cracking and separation of phases [5].

Uniformity of weight

Five films of each formulation were weighed individually on a precision electronic balance (GEHAKA® MOD. B64001).

Resistance to folding (Flexibility)

Three films from each batch were randomly selected to measure the resistance to folding. The films were repeatedly folded in the same place until it broke or even the size no longer foldable. At the end of the process, the formulations that were not broken were considered satisfactory.

Disintegration test

The methodology described in the Brazilian Pharmacopoeia [9] was used for the disintegration test of tablets and capsules with modifications. Three films of each formulation were embedded in each well of the Disintegrator with tub (NOVA ETHICS MOD 301-AC) immersed in 700 ml of Phosphate buffer solution pH 6.8, at a temperature of 37°C, under stirring, for 1 h and 30 minutes.

Surface pH

Surface pH was measured with the use of pH indicator paper placed on the surface of the swollen film.

Swelling test

Water absorption was determined by gravimetry [1]. The dried films attached to the stainless steel support were immersed in a beaker with distilled water (60 mL) at room temperature for 1 hour. At specific intervals (10, 20, 30, 40 and 60 minutes), the supports with the swollen samples were weighed after removal of the water. The percent swelling index was calculated by the following equation 1

W_i is the weight of dry film and W_f is the weight after the swelling.

Equation 1: $G_I = W_f - W_i \times 100 \backslash W_i$

Where: G_I is the degree of swelling in (%), W_f is the final weight at each of the times; W_i initial mass of the dry film.

Development of oral membranes with Chlorhexidine 0.12%

Formulations selected as promising for the controlled release of drugs were reproduced as described above and 0.12% of Chlorhexidine was added in the cooling step. At the end of the process, the formulations were individually distributed by weight on an acrylic plate with marked spaces for each film and stored in an oven (LABTRADE® MOD. EB100) at 37°C (± 2°C) for a period of 24 hours.

Uniformity of content

The content uniformity of the chlorhexidine was determined by dissolving the films in 100 ml phosphate buffer pH 6.8 for 2 h under 50 rpm shaking. The content of chlorhexidine was determined by means of the absorbance at 257 nm on a UV-visible spectrophotometer. The assay was performed by triplicate.

Dissolution test

The assay was performed under sink conditions. For the in vitro release study, 100 ml of phosphate buffer pH 6.8, maintained at 37 ± 0.50°C less than 100 rpm stirring was

used. Aliquots of samples (5 mL) were drawn at 5, 15, 30, 60, 90, 120, 150, 180 and 240 minutes intervals. Concentration of the drug released in the medium was measured by UV-visible spectrophotometry at 257 nm.

Results

Macroscopic analysis

Table 2 shows the characteristics evaluated and the results evidenced

Weight uniformity

The greater the amount of polymer the greater the final weight of the film. F1 and F2 presented the lowest weight and are the formulations that have less amount of polymer, represented by only 4% of starch. On the other hand, the other formulations have 5% of polymer and as the concentration of starch in the formulation increases there is an increase in the final weight of the films.

Disintegration test

The disintegration test was carried out for 1h and 30min and at the end of that time none of the formulations completely disintegrated, however, at the end of the test all the films were weighed and the mass loss in % proportional of the test time performed was obtained. The results are shown in *Table 2*. F1 and F2 obtained a loss of mass of 70.5% and 77.3%, respectively, whereas for F3, F4 and F5 a loss of 47.8%, 39.1% and 31.8% was obtained. F6 lost only 22.3% of its initial weight.

Comparing F1 and F2 the results show that the concentration of sorbitol influenced the increase of the solubility of the starch favoring its rapid disintegration, since for both there was a loss of weight of 72.5% and 77.3%, respectively. However, when the polymer concentration is increased to 5%, the films disintegration times are significantly reduced, and as the concentration of Chondroitin Sulfate over the starch in the larger formulation is increased, the resistance of such films to the rapid disintegration is increased.

Table 2. Macroscopic evaluation of the films produced.

Characteristic	F	F1	F2	F3	F4	F5	F6
Macroscopic Evaluation	Colour	Glassy	Glassy	Glassy	white	white	white
	bubbles	+	-	-	-	-	-
	Cracks	+	-	-	-	+	-
Weight Uniformity (mg)	-	11,05 ± 0,75	97,23 ± 2,75	115,22 ± 1,35	110,12 ± 0,95	109,25 ± 1,08	105,78 ± 1,82
Flexibility	-	+	+++	+++	+++	++	+++
Desintegration (% loss of weight)	-	70,5	77,3	47,8	39,1	31,8	22,3
pH	-	6,56	6,85	7,67	6,20	6,07	6,05
- Absence + Slightly Present ++ Medium Present +++ Strongly present							

Surface pH

The results show that the pH of the films is compatible with the mouth and is related to the amount of starch in the film.

It is observed that the formulations had a slightly acidic pH, except for the formulation F3 which presented a greater amount of starch in its composition.

Swelling test

The degree of swelling was evaluated for 1 hour at times 10, 20, 30, 40 and 60 min to determine the degree of hydration of the films. These tests demonstrated, according to *Figure 1* that, despite the changes presented, there was a period of hydration equilibrium for practically all formulations between 10 and 60 min.

Evaluating the formulations F4, F5 and F6, produced with the association of the polymers starch and CS, it was observed that all behaved in a similar way in the swelling test. F4 swelled faster in the first 20 minutes, however over the course of 60 minutes its swelling degree was lower than the other formulations. Behavior similar to F3, which swelled rapidly and then the degree of swelling was decreasing, a hypothesis for this behavior may be the presence of a large amount of starch, since among the films produced with the addition of CS, F4 is composed of 90% starch and 10% CS, thus having the highest amount of starch. The F5 and F6 formulations presented a very similar degree of swelling, both of which presented a more uniform swelling degree, and F5 presented a more gradual and increasing hydration capacity over time. The swelling is the result of a balance between the dispersion forces and the cohesive forces acting on the hydrated chains due to the cross-covalent bonds. This suggests that the hydration of the starch is controlled by the presence of CS, and that the ideal formulations for chlorhexidine-modified films would be formulations F5 and F6 with 5% of the polymer solution, associating starch and CS in the proportions of 85: 15 and 80:20, respectively.

Analyzing *Figure 1*, it is observed that the F1 film presented a high hydration peak in the first 10 minutes, and that during the 60 min its hydration remained practically constant.

Also, analyzing *Figure 1*, it is observed that the highest swelling peaks occur in the first 20 minutes (formulations 1, 2 and 3) and 30 minutes (formulations 4, 5 and 6).

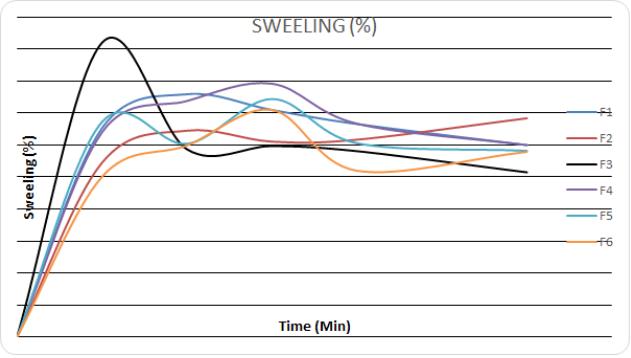

Figure 1. *Graphical represent showing percent swelling of films versus minute.*

Uniformity of content

After the previous tests, the formulations F5 and F6 were selected to be reproduced again, this time with the addition of 0.12% of chlorhexidine, denominated, respectively, FC5 and FC6.

First, a calibration curve was performed with chlorhexidine and the following equation of the line y=0.7693X-0.001 was obtained with R2=0.9709. From this equation of the line the following results of chlorhexidine content were obtained for formulations FC5 and FC6 *Table 3*.

Table 3*. Chlorhexidine content results.*

	FC5(%)	FC6 (%)
Average (n=5)	97,6	98,24
Standard Deviation	1,67	0,83

Dissolution test

In *Figure 2*, it can be seen that both formulations FC5 and FC6 were able to exert a control over the release of chlorhexidine for 4 hours. The presence of Chondroitin Sulfate was responsible for the control of the hydrophilicity of the starch and, in turn, responsible for the control of the release of the active.

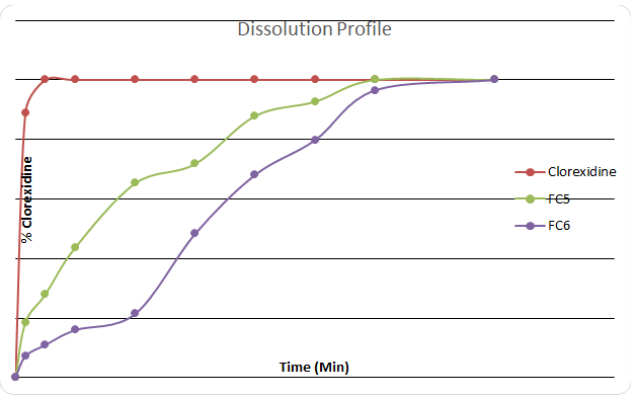

Figure 2. *Graphical represent showing Percent Clorexidine versus minute.*

Discussion

According to Bunhak et al. [5], the analysis of the macroscopic and morphological characteristics, especially with respect to transparency, presence of air bubbles and cracking is of fundamental importance since the integrity of the films obtained influences the quality of the same.

Formulations F1, F2 and F3 consisting solely of starch and sorbitol, were shown to be more transparent than the increased formulations of CS. This suggests that the presence of CS increases the degree of opacity of the product under study, since the formulations F4, F5 and F6 were more opaque than the others. It was also observed that the higher the amount of starch, the lower the degree of transparency, since formulations 1 and 2, with 4% w/w starch, was more transparent than F3, with 5% of the same polymer. The visual appearance of the films was affected by the polymer content and the presence of CS, but the proportion of plasticizer did not influence the opacity of the film, since F1 and F2 remained with the same transparency content.

Transparency is generally desirable when the film is applied for food coating, since it does not block the product visualization, and can be used in a situation where the conditioned product should be observed by the consumer, since it can perfectly identify any object placed under the films.

Regarding flexibility, the formulation F1, developed with 20% of sorbitol was the most brittle of all, since the number of folds was well inferior to the formulations F2, F3, F4, F5 and F6, since all the latter had flexible folds until the end point of no longer taking action. This result indicates that the proportion of the plasticizer is one of the critical parameters for achieving good film elongation. Mali et al. [10] stated that plasticizers are responsible for giving greater flexibility to the polymer structure, increasing the mobility of the starch chains and reducing the stiffness of the material. Thus, they favor the transition of the material from a vitreous state, characterized by a lower molecular mobility between the polymer chains and by a higher stiffness, to a rubbery or gummy state, of greater molecular mobility and, consequently, greater flexibility [11]. However, if the plasticizer is used in a very small amount, below 20%, it may not exert its effects, and act as an anti-plasticizer [10].

The flexibility of the material is an important feature where high elongation is a decisive factor for its use as a coating film. For controlled drug release buccal membranes, the low mechanical resistance thereof is unacceptable, since brittle membranes can lead to rapid and discontinuous release of the drug.

The weight increase found in the formulations as the starch concentration is increased can be explained by its high molecular weight in comparison to the other pharmaceutical excipients of the formulation, not interfering in its performance as a drug delivery system [12].

Regarding the surface pH of the films, all formulations presented a slightly acidic character, with only F3 having a slightly alkaline pH. It should be noted that such pH changes would not generate large clinical repercussions, since all pH

ranges of the formulations are suitable for a drug delivery system in the oral cavity [12].

Controlled release of drugs through polymer films is determined by the dissolution properties of the film in the gastrointestinal tract or by the permeability to gastrointestinal fluids.

Formulations F1 and F2, consisting of 4% of starch degraded faster than the other batches with 5% of film-forming solution, suggesting that the higher the content of polymer the more compact the membrane, and therefore the more difficult the permeation of the solvent through the film, with less degradation. The presence of CS in the membranes decreased the hydrophilicity of the starch, and the higher the CS w / w content per polymer, the greater the resistance to degradation. These results may be related to the high molecular weight of CS, which consequently interacts less with water [13]. Similarly, Borges [1] states that the reduced molecular mass of a polymer interacts more with water and for that reason, it was evaluated that the addition of hydrolyzed collagen in membranes of oral disintegration, considerably increased the disintegration time of the films, and this behavior was related to the reduced molecular mass of the hydrolyzed collagen, which consequently increased its interaction with water.

One of the drawbacks of starch-based films is their high hydrophilicity. Its rapid absorption of water causes the material to swell and rupture, which may disrupt its mechanical and barrier properties. This starch property encourages the search for alternatives to decrease its hydrophilic properties [14]. With the results presented, the unprecedented association of starch with CS can be considered promising for the development of films that need to maintain their structural integrity during their function.

Marcio et al. [15] evaluated antibiotic-containing membranes for tissue regeneration and have stated that films need to maintain their structural integrity to function as wound protection; otherwise treatment may fail regardless of whether it has been competent to maintain the pathogen-free regeneration site aggressive.

The degree of swelling for the evaluated lots presented low values. For all formulations over the course of 60 minutes the mean swelling was around 6.5%. This low value of swelling (%) of the membranes evaluated in 1 hour is confirming the results of non-degradation of the membranes in 1 hour and 30 minutes, since, the evaluation of the swelling index in isolated films allows to verify in advance the perspective of degradation, which is related to the degree of hydration of the system, while the release of the drug is also intrinsically dependent on membrane permeability.

The initial swelling verified in *Figure 1* can be justified by the high hydrophilicity of the starch since that of all films evaluated, formulation 3 is the one containing the largest amount of starch, 5%, and this may have generated immediate hydration of the formulation, reaching its peak of swelling already in the first 10 minutes.

This high absorption rate is a disadvantage for such films, since a rapid absorption of water brings undesirable consequences such as the reduction of the stability of the polymer. This is because the constant presence of moisture in the polymer structure causes the matrix to swell, leading to fiber disintegration and accelerating the degradation process by microorganism attack [16].

Comparing the F2 and F3 formulations, both with starch and sorbitol, varying only the concentration of the polymer, it is observed that the higher the percentage of starch, the faster the swelling, i.e., the hydration capacity increases with the starch concentration in the formulation. Matta Junior et al. [2] also observed in their studies that the increase of the concentration of the pea starch in the filmogenic solution increased the hydration of these films.

Another important factor in starch films is the influence of plasticizer. If we evaluate the formulations F1 and F2, both with the same amount of starch and different concentrations of plasticizer, it is observed that the formulation with greater amount of sorbitol (F2) had a higher percentage of swelling, although the F1 presented a peak in 30 minutes greater than that presented by F2. This can be explained by the hydrophilic character of the plasticizer, which facilitates the hydration of the polymer. These results were also found by Matta Junior [2] where he reports in his studies that the films that presented lower solubility were those produced without plasticizer.

Fernandes [16] observed in his studies with membranes based on chitosan and CS that there was a decrease in the degree of swelling with time. In the first hour the degree of swelling reaches its apex and apparently after this period the films reach a balance in the process of water absorption. Bunhak et al. [5] also observed in their studies this tendency to reach the hydration balance. He developed polymethacrylate membranes with CS, and observed that despite the changes presented, there was a period of hydration equilibrium for virtually all compositions between 10 and 60 min. The same occurred in this study, where a peak was observed around 30 minutes in the degree of swelling, followed by a gradual reduction of this rate in the rest of the time.

The results of the drug content show that the methodology is efficient and robust in the production of biodegradable chlorhexidine films since in addition to being uniform the methodology used did not degrade the active.

Conclusion

The results of this work demonstrated that it is possible to develop films based on starch and starch with chondroitin sulfate from simple techniques with good flexibility properties and homogeneous surfaces evidenced by the absence of bubbles and cracks. Future studies will be performed with the addition of dyes or flavorings with the aim of improving their sensory characteristics.

The low hydration capacity of the evaluated films becomes a positive factor for the development of coating films, since its application involves exposure to the environment, and this characteristic increases its stability to microorganisms.

The degradation of the films was considered slow, which makes them promising for several applications, including controlled release films. For this application, lots 5 and 6 were considered the most appropriate.

It is believed that this pharmaceutical form can be a promising vehicle to deliver drug with activity in the oral cavity, and it may be possible to develop products with therapeutic potential in a range of clinical situations: from the prevention of dental caries to the treatment of local inflammation.

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