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ORIGINAL ARTICLE

Characterization of low cost orally disintegrating film (ODF)

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Abstract

Orally disintegrating films (ODF) produced with a hydrophilic polymers are a thin and flexible material, wich disintegrate in contact with saliva and can vehicule bioactive materials. The aim of this study was to develop and characterize ODF formulation with potential to act as a carrier for different bioactives compounds prepared with low cost polymers. Gelatin (G), starch (S), carboxymethyl cellulose (CMC) and their blends (G:S, CMC:S, CMC:G, and CMC:S:G) were prepared by casting technique with sorbitol as a plasticizer. The formulations were characterized in terms of visual aspects, FTIR, SEM, mechanical characteristics, hygroscopicity, dissolution (in vitro and in vivo) and swelling index. FTIR analysis revealed that no interaction between polymers in ODF was observed. By SEM, it was possible to observe differences on surfaces by different polymers. ODF made with CMC and CMC:G presented higher water absorption ($P<0.05$) and higher swelling index probably due to the higher water affinity by CMC. Formulations with G, CMC:G and CMC:S:G presented the highest values of tensile strength ($P<0.05$). ODF prepared with S alone presented the highest disintegration time, the others formulations showed in vitro dissolution ranging from 5.22 to 8.50 min, while in vivo dissolution time ranged from 2.15 to 3.38 min. By the formulations made with G and blend of G:S and CMC:S:G it is possible to develop a ODF of low cost with desired characteristics being an alternative vehicle to deliver functional compounds for continuous use.

Keywords: *biofilm, dissolution, polymeric matrix, oral vehicle.*

1. Introduction

Edible films produced by natural macromolecules have emerged as a potential product for the food industry to protect fruits and for its possible application as biodegradable packaging. However, the pharmaceutical industry has used the same technology to a different application. Orally disintegrating films (ODF) presented as strips derived from hydrophilic polymers that dissolve in oral cavity can delivery drugs and bioactive compounds such as caffeine, nicotine, drugs, refreshing compounds, vitamins, minerals and probiotics[1-4].

The advantage of using ODF is the high efficiency of absorption of some compounds by oral via without the need of water for swallow, being an alternative to bioactive administered in tablets and pills[1,3], and moreover the absorption through the buccal epithelium, without contact with gastrointestinal tract which could degrade some sensible compounds[5]. Moreover, some peoples have difficulty in take and dissolve tablets and capsules, once those materials are larger and necessity a strong buccal work to disintegrate and dissolving the drug or bioactive compost[6]. Therefore, the use of strips for oral dissolution presents some advantages, but development should take into consideration sensory characteristics of the product.

A variety of biopolymers can be used for oral strips formation, alone or in blends. An alginate/gelatin blend film was developed and this considered a potentially useful in drug delivery systems[7]. Films produced with gelatin, polyvinyl alcohol and carboxyvinyl turn into a jelly in contact with small amounts of saliva, passed through esophagus and reached the stomach more quickly than a gelatin capsule[8]. Other researchers have used microcrystalline cellulose, hydroxypropylmethyl cellulose and carboxymethyl cellulose as base materials to prepare oral film[9,10]. The most common technique for film production is casting. It is based on the dispersion of a biopolymers in a solvent (water, ethanol and organic acids), addition of additives (plasticizers), yielding a solution that undergoes drying operation[3,5].

The ODF formulation should be hard enough to not be damaged during handling and transportation, and present suitably disintegration in the mouth, but these features depends on polymeric composition[3,11]. In order to support the stress in the mouth, an ideal oral film should be strong and yet, flexible, elastic, and soft[9,12]. In this way, in order to use those ODF as a material of controlled release it is firstly necessary to better understanding their properties as model, without bioactive compounds or drugs, for its future application.

Therefore, the objective of this study was to develop ODF's using low cost polymers, and characterize those materials in terms of some factors that may have influence on the drug release, as visual, mechanical and microstructure characteristics, higroscopicity, swelling and disintegration properties. The material developed could be a successful application for drug delivery or bioactive controlled release in vivo or different industry process.

2. Materials and Methods

2.1 Materials for preparation of ODF

Formulations were prepared using cassava starch (ARGO CC3400, Corn Products, Brazil); type A gelatin (260 Bloom/ 30 mesh) (Gelita do Brasil, São Paulo-Brazil); carboxymethyl cellulose (CMC 30000, Plury Química, Brazil) and sorbitol (Synth, Brazil). All the listed ingredients are considered GRAS (Generally Recognized as Safe) for FDA (Food And Drug Administration) and allowed for food products preparation..

2.2 Preparation of polymer matrix

For ODF production it was used different combinations of the macromolecules gelatin (G), starch (S), and carboxymethyl cellulose (CMC) according to Table 1. Sorbitol concentration, the plasticizer, was kept constant at 20 g/100 g of macromolecules. Macromolecules and plasticizer concentration were defined in according to preliminary tests. ODF's were prepared by casting technique.

For starch ODF production, 2 g of starch was dispersed in 100 mL of distilled water for 20 min. Then the solution was heated with constant magnetic stirring (Marconi, MA085 – Brazil) until reached 75 °C/ 20 min. Then sorbitol mass (20 g/ 100 g of macromolecules) was added. For gelatin formulation, the same protocol was followed. For CMC formulation (1 g of CMC/ 100 mL), the carbohydrate was solubilized in water and was stirred overnight in order to avoid macromolecule insolubilization. Then, sorbitol was added and the final concentration was corrected with the addition of water.

For the development of binary blends CMC:S, CMC:G, G:S, and CMC:S:G, the corresponding solution of each polymer was prepared as previously described. Then, the solutions were mixed according to the concentrations described in Table 1 added by sorbitol mass.

In order to avoid bubbles in ODF, all formulations were placed for 10 min in ultrasonic bath and then poured on acrylic plates (12 × 12 cm), according to a previously standardized mass to ensure uniform thickness after drying. Drying of different formulation was in air forced oven at 30 °C/ 24 to 48 h (Marconi, MA035/5 – Brazil). After drying, the films were carefully removed from plates and placed in desiccators (NaBr saline saturated solution, relative humidity = 58%) at 25 °C for at least 48 h until analysis. The thickness of each strips was measured using digital micrometer (Mitutoyo), considering the average of at least nine values[13].

Table 1. Composition of orally disintegrating films (ODF) formulations produced with gelatin (G), starch (S) or carboxymethyl cellulose (CMC), or its blends.

Formulation	Composition (%)		
	Gelatin solution (2 g/100mL)	Starch solution (2 g/100mL)	CMC solution (1 g/100mL)
G	100	0	0
S	0	100	0
CMC	0	0	100
G:S	50	50	0
CMC:S	0	80	20
CMC:G	80	0	20
CMC:S:G	40	40	20

The overall aspects of the product were evaluated, considering its homogeneity, easiness of peeling from acrylic plate and presence of bubbles or grumps.

2.3 Scanning electron microscopy (SEM)

For this analysis, 1 × 1 cm samples were cut from strips, cryofractured and mounted in copper stubs. Samples were gold coated. The internal structure of the sample was evaluated using a Jeol scanning electron microscope (JMS-T300, Tokyo, Japan) at 5kV in a climatized room[14]. Before this tests, ODFs were stored in desiccators containing silica gel for 10 days.

2.4 FTIR

The infrared spectra (FTIR) of the ODF were recorded between 600 and 4000 cm^{-1} and at 4 cm^{-1} of resolution with a Spectrum One (Perkin Elmer, Shelton, CT, USA) spectrometer[15]. For each spectrum, 16 scans were co-added. Before this tests, ODFs were stored in desiccators containing silica gel for 10 days.

2.5 Mechanical properties

The mechanical properties of ODF were evaluated by tensile test [TS = tensile strength (MPa) and E= elongation at break (%)] using a texturometer TA.XT2i (Stable Micro Systems, UK)[16]. Samples of the films (12.0 × 2.54 cm) were fixed on a specific probe (tensile grips), at an initial separation distance of 100 mm, and test speed was constant at 50 mm/ min.

2.6 Moisture and hygroscopicity evaluation

The moisture evaluation was performed in a high-precision moisture analyzer (Ohaus MB35 - USA) by infrared radiation from a halogen source[17]. To determine the hygroscopicity, 1g samples of each formulation was placed on glass slides, where were conditioned by 25 °C/ 7 days in desiccators with saturated solution of Na_2SO_4 (RH 81%). The hygroscopicity was determined by the water mass absorbed by the sample[18].

2.7 Swelling index

Samples of 2 × 2 cm of different formulations (140-160 mg) were placed in a metal sieve and immersed in 40 mL of saliva simulated solution[19] in water bath at 36 ± 2 °C, according to adapted procedures[9]. The samples were weighed every 30 seconds until the maximum absorption of water was reached. The swollen weight of the strips was performed. The swelling index was calculated as the ratio between the masses of the strips after and before immersion, respectively.

2.8 In vitro disintegration time

The ODF's disintegration time were evaluated according to previous developed method[20] with some modifications. For this, pieces of 2 × 3 cm of each formulation (0.17 to 0.20 mg) were placed in 50 mL of simulated saliva solution, in a water

bath at 36 ± 2 °C with mechanical stirring. The time for complete disintegration was visually evaluated. An average of triplicated analysis of each formulation was performed.

2.9 In vivo disintegration time

An assay to evaluate differences in disintegration time of different formulations was conducted. For this evaluation, 17 panelists were recruited (5 males and 12 females; ages between 19 and 41) and trained on how to evaluate the desintegration time of samples.

Panelists were conducted to individual cabinet where 3 × 2 cm samples were randomly served. A chronometer was used for panelists determine the time until the complete disintegration of the sample in the mouth.

This study was conducted in accordance with ethical principles and approved by FZEA-USP ethical committee (Process 2010.1.1479.74.3). Prior to performing the test, panelists signed a free and informed consent term.

2.10 Statistical analysis

All experiments were performed in triplicate. The data were statistically analyzed using SAS version 9.2, by ANOVA followed by Tukey test (5% of significance).

3. Results and Discussions

All samples were homogenous, without bubbles and phase separation. It was possible to produce oral strips with the different tested formulations, but the formulation using only starch was difficult to be peeled of, breaking easily. ODF produced with G and CMC were brilliant and the ones with S in composition were opaque.

3.1 SEM analysis

The structure characteristics of the different formulations evaluated are shown in Figure 1. Differences could be observed in the surface structure of different polymers. ODF produced with the blend carboxymethil cellulose: cassava starch (Figure 1F), and carboxymethil cellulose: cassava starch: gelatin (Figure 1G) presented roughness in the surface. All other blends (Figure 1D e 1E) and polymers alone (Figure 1A, 1B and 1C) presented very homogeneous surface. Roughness at surface in films made with starch blends has already observed, in general, the micrograph cross section of cassava starch-based films displayed an irregular and rough structure[21]. The authors suggested that this heterogeneous structure could be due to the retrogradation and partial crystallization of gelatinized starch before the formation of the film. The micrograph results suggested good compatibility among the polymers, without micro phase separation, however starch in combination with other polymers, presented surface modification in rugosity.

3.2 FTIR analysis

FTIR spectroscopy was used to examine the interactions between macromolecules used to prepare the ODF. The infrared spectra of CMC, gelatin and starch, and their blends are represented in Figure 2. The spectrum of CMC, starch and gelatin alone were similar to previous reported in the literature[15,22,23]. For CMC characteristic band were observed at 1587 cm^{-1} (stretching of C=O), 1415 cm^{-1} (CH2 carboxylic groups), 1322 cm^{-1} (absorption of CH2) e 1051 cm^{-1} (stretching of C-O), consistent with previous data reported[22]. For gelatin alone, band centered around 3300 cm^{-1} is mainly due to the extension of the group NH of amide A. In the range 3000-3500 cm^{-1} there is a absorption band due to hydroxyl groups (OH), in the films of S:G. Its intensity decreases, indicating that the polymer created linkages of hydrogen intra chains. The intense bands between 1700 and 1600 cm^{-1} and between 1600 and 1500 cm^{-1}, are known, respectively, as bands of amide I and amide II. Amide III, with bands between 1200 and 1400 cm^{-1}, represent components of the extension of C–N and N-H and absorptions resulting from the vibrations of groups C–H2 of the glycine and proline[23]. Starch oral film also presents similar FTIR spectra from the one previous presented[15].

When two or more substances are mixed, physical blends versus chemical interactions are reflected by changes in characteristic spectra peaks[24,25]. Apparently, no structural changes occurred since the peaks of the blends broads compared to the ones with single polymers were similar. The results suggest that the formation of new bonds between macromolecules for blends formulation of ODF do not occur.

3.3 Mechanical properties

The Table 2 present the results of tensile strength and elongation obtained from ODF prepared G, S, CMC and their blends. It could be observed (Table 2) that the ODF with gelatin in the formulation presented higher tensile strength and elongation, compared to the others formulations (S, CMC and CMC:S). Probably, the improvements observed in ODF containing gelatin are a consequence of the high cohesivity of the polymeric matrix.

Similar values of the tensile strength reported in this study were observed for ODF's made with pullulan, sodium alginate and CMC blends[26]. Gelatin:alginate oral strips, produced for controlled drugs release, presented values of maximum tensile strength and elongation when the blend of gelatin and alginate was 50%[7]. The authors observed that increasing gelatin or alginate content rather than 50% decreased the tensile strength.

Table 2. Mechanical properties of orally disintegrating films (ODF) produced with gelatin (G), starch (S) or carboxymethyl celulose (CMC), or its blends (means ± standard deviation)*.

OFD identification	Tensile strength (MPa)	Elongation (%)
G	55.81 ± 5.15 ^{a,b}	7.40 ± 1.67 ^{a,b}
S	22.47 ± 5.93 ^{d}	5.40 ± 1.43 ^{a,b}
CMC	34.61 ± 9.35 ^{c,d}	5.78 ± 2.91 ^{a,b}
G:S	47.49 ± 3.82 ^{b,c}	4.86 ± 1.56 ^{a,b}
CMC:G	71.72 ± 9.08 ^{a}	8.95 ± 1.75 ^{a}
CMC:S	32.03 ± 6.27 ^{c,d}	3.60 ± 1.11 ^{b}
CMC:S:G	49.29 ± 2.53 ^{b,c}	7.49 ± 2.59 ^{a,b}

*Means followed by the same letter in each column are not different according to tuckey's test ($p \leq 0.05$).

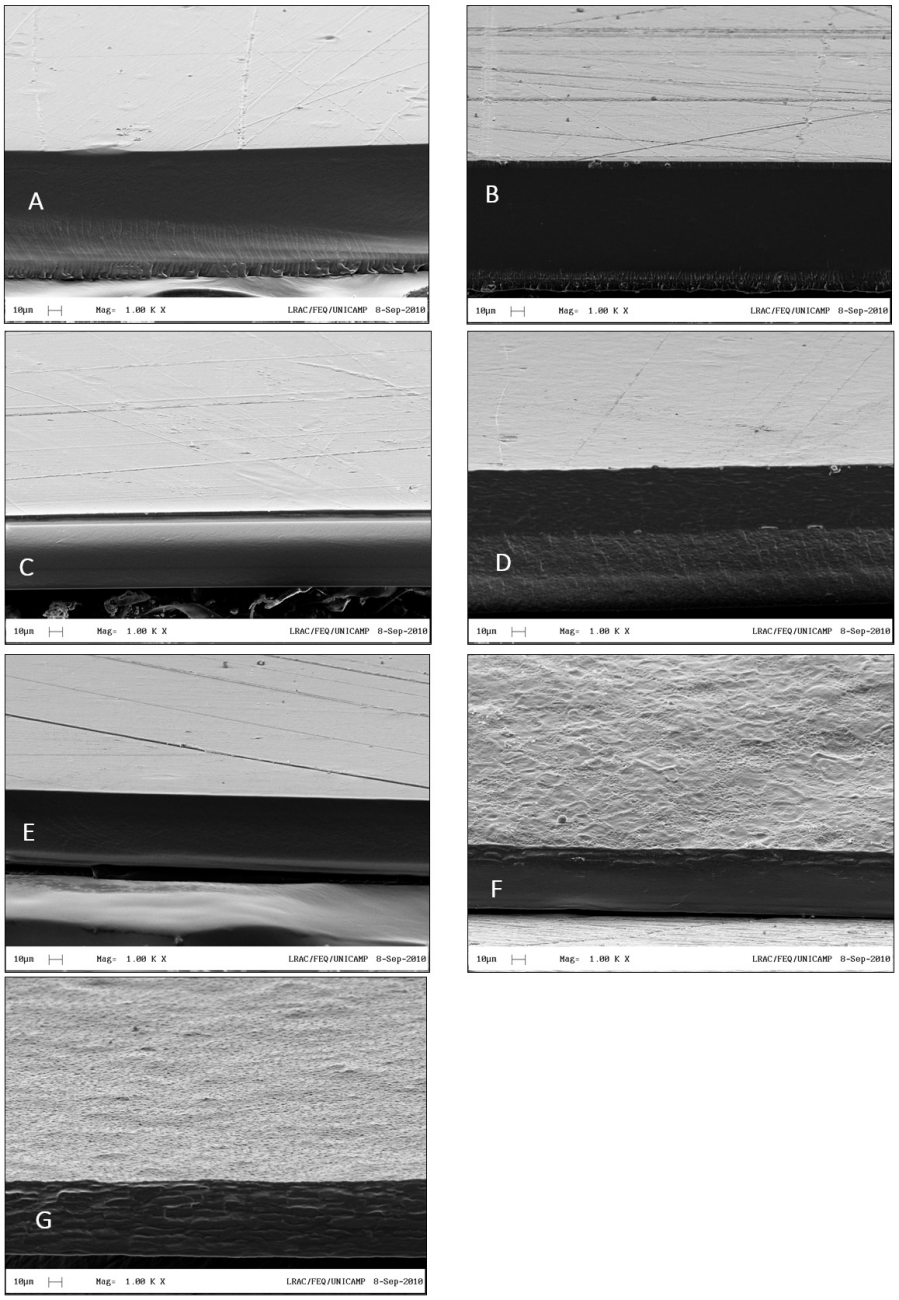

Figure 1. Micrographs of orally disintegrating films (ODF): (A) gelatin (G); (B) cassava starch (S); (C) carboxymethil cellulose (CMC); (D) gelatin: cassava starch (G:S); (E) carboxymethil cellulose: gelatin (CMC:G); (F) carboxymethil cellulose: cassava starch (CMC:S); (G) carboxymethil cellulose: cassava starch: gelatin (CMC:S:G).

3.4 Hygroscopicity and swelling index

Table 3 presented the values of hygroscopicity and swelling index from the different ODF formulations.

The hygroscopicity is the amount of absorbed water under controlled conditions at high RH. From the results obtained it could be observed that the hygroscopic of ODF ranged from 12.6 g / 100g to 31.5 g / 100g (Table 3). All formulations absorbed water after one week storage, but the ODF composed of only CMC and CMC:G showed the highest values, ~31.4 g / 100 g ($P< 0.05$); it was also observed that these strips were sticky. The ODF produced with only G or S presented the lower hygroscopity. Their average value was only 14.8 g /100 g, significantly lower than the others ODF hygroscopic. The strips composed of the ternary blend CMC:S:G presented intermediate values of hygroscopicity, and, were not sticky. This diference in water adsorption could be related to the number of hydrophilic groups present in the structure of each agent[27], or to the number of active sites to linkage of water. There is no

information in the literature about hygroscopicity behavior recommended for storage of ODF.

On other hand, the production of ODF with only carboxymethil celloluse, or in a blend with gelatin, could improve the final material hygroscopicity, which is not desirable. Therefore, these formulations were not evaluated in terms of dissolution in vivo.

In relation to the swelling index (Table 3) it could be observed from the different ODF formulations a greatly variation depending on their composition, with water absorption values from 4.08 to 17.71 g of water/g. Strips composed of S, G and G:S showed the lowest capacity of swelling ($P < 0.05$). Strips composed by CMC presented the highest capacity of swelling ($P < 0.05$), differing from the others. When CMC was incorporated to the formulation, in relation to S or G formulation, the ODF water affinity was enhanced

The CMC affinity with water was observed when reduced contents of carbopol (cross-linked polyacrylate polymer) and increased sodium carboxymethyl cellulose contents were applied for strips production, and the swelling index also increased[28]. This effect was also observed with the increase of sodium carboxymethyl cellulose contents[9]. Bajpai and Shrivastava[29] observed the same effect in polymeric film made with crosslinked starch and carboxymethyl cellulose, the increase of CMC concentration increased the sweeling of films. CMC is a modified natural water-soluble polymer, wich contains hydroxy and carboxyl groups, and therefore improve hydrophilicity to the molecule[29], which could explain the minor levels of sweeling index of ODF's produced without CMC.

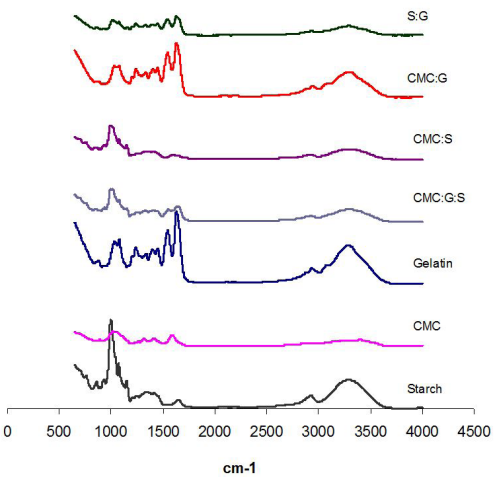

Figure 2. FTIR spectra of gelatin (G), starch (S), carboximethil celulose (CMC) and their blends in orally disintegrating films (ODF).

If the swelling of films exists, it should not be to extensive in order to prevent discomfort[9]. In this way, again the ODF contain only CMC and CMC:G were discarded, and therefore not considered for in vivo analyses.

3.5 In vitro disintegration time

Some authors developed fast dissolving oral films[2,11,30], while others bioadhesive films[9,28] which can that take minutes or hours to release the active compound of interest. No official guidance time is referenced for oral fast disintegrating films/strips[1,3]. In the same way, no official time for disintegration of ODF was found. Therefore, in this paper, it was established the time of 4 min as the ideal for the in vitro disintegration of oral strips, as the time that allows gradual release of bioactive compounds to be added, without causing fatigue to the consumer.

According to Table 3, starch ODF showed the highest disintegration time, > 100 min. It was observed that after 24 h/ 36 °C in the presence of simulated saliva it still remained intact, therefore without interest for the development of active compounds in an oral vehicle. Furthermore, even if a saliva with enzyme could be used, this probably would not reduce sufficient the in vitro disintegration time in order to be possible to select this ODF for in vivo analyses (see reduction time for ODF produced with starch blends). The others formulations showed disintegration time ranging from 5.22 to 8.50 min. Visually, it was observed that the formulation with only S and with CMC:S breakdown in small pieces and did not completely dissolve in the solution. The others formed a continue phase with water. The results are in the same magnitude order then ODF produced with gelatin and hydrolyzed collagen[31], which varied from ~ 6 to 9 minutes in function of hydrolyzed collagen concentration.

Therefore, in accordance to in vitro dissolution time, ODF's produced with only S, and the blend CMC:S, were not considered adequate. Thus, only G, G:S, CMC:G:S ODF's were characterized in relation to in vivo disintegration time.

Table 3. Characterization parameters of orally disintegrating films (ODF) produced with gelatin (G), starch (S) or carboxymethyl celulose (CMC), or its blends (mean ± standard deviation)*.

ODF identification	Moisture ($g\ H_2O/g$)	Hygroscopicity ($g\ H_2O/g$)	Swelling index ($g\ H_2O/g$)	In vitro disintegration time (min)
G	11.43 ± 0.74^{b}	$16.90 \pm 1.16^{c,d}$	4.83 ± 0.78^{d}	5.22 ± 0.20^{d}
S	9.95 ± 0.61^{b}	12.61 ± 1.89^{d}	4.08 ± 0.45^{d}	$>100^{a}$
CMC	15.17 ± 1.46^{a}	31.25 ± 4.92^{a}	17.71 ± 0.35^{a}	6.07 ± 1.21^{d}
G:S	11.49 ± 0.86^{b}	23.32 ± 0.49^{b}	4.37 ± 0.34^{d}	$7.96 \pm 0.56^{b,c}$
CMC:G	10.97 ± 0.41^{b}	31.49 ± 2.75^{a}	13.46 ± 2.86^{b}	8.50 ± 0.60^{b}
CMC:S	9.95 ± 0.57^{b}	23.18 ± 0.91^{b}	8.96 ± 0.40^{c}	$8.37 \pm 1.12^{b,c}$
CMC:S:G	11.01 ± 0.09^{b}	$18.75 \pm 1.10^{b,c}$	8.20 ± 1.06^{c}	$6.50 \pm 0.67^{c,d}$

*Means followed by the same letter in each column are not signicantly different according to tuckey's test ($P < 0.05$).

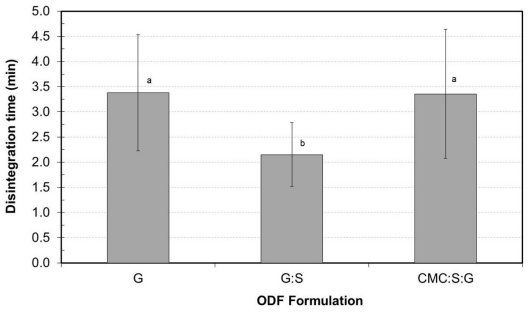

Figure 3. *In vivo* disintegration time of different orally-disintegrating film (ODF) produced with gelatin (G), gelatin:cassava starch (G:S), and carboxymethyl cellulose:cassava starch:gelatin (CMC:S:G). Different lowercase letters indicate a significant difference ($p < 0.05$) between the different formulations of ODF.

3.6 In vivo disintegration time

In vivo test with three formulations was evaluated and results could be observed in Figure 3. The means of disintegration time varied between 2.15 and 3.38 min. The in vivo disintegration test showed that all panelists agreed that the dissolution of samples was comfort to them; however, as expected for in vivo tests, there was great variability in the results. It could be observed that the disintegration times of the test in vivo were lower than the in vitro test, probably due to a lack in enzymatic activity and mechanical action of the second. Few studies report the disintegration time of oral strips. Oral strips produced with maltodextrin presented in vivo disintegration of only 10 s[30]. For ODF based on hydroxypropyl methylcellulose, corn starch, polyethylene glycol, and lactose monohydrate with donepezil a disintegration mean time of 49 s[32]. For drug delivery by oral route, an ODF with hydroxy-propyl methyl cellulose and carbopol had a residence time of 23 min[9].

The disintegration time will depend on the characteristic of the bioactive or drug released[2]. Some compounds should be continued released, while others should be immediately absorbed. In this study, during the development was set the objective of gradual release of a hydrophilic bioactive as vitamins or minerals, but fast enough to do not cause stress to the consumer. This parameter was achieved with all tested formulations in vivo study.

4. Conclusions

The study showed that the composition of ODF had important relevant influence on properties evaluated, and therefore probably on the ODF release properties. Gelatin, cassava starch, carboxymethyl cellulose, and its blends, were successful applied for ODF production by "casting" technique. However, ODF's produced with only starch were not interesting due to difficulty in handling and slow time disintegration (> 100 min). ODF's composed with only CMC, and blends of CMC:G were very sticky and therefore were discarded. On the other hand, formulations made by G, G:S and CMC:S:G were more suitable for ODF production, since it was homogeneous, presented average values of hygroscopicity, good performance in mechanical tests and an acepatble in vivo disintegration time, with no uncomfortable sensation. Therefore, those ODF could be very useful for an innovative oral vehicle for controlled release of bioactives compounds.

5. Acknowledgements

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