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Article

Starch-based orodispersible film for diclofenac release

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The form of drug administration affects the success of treatment, since it can influence adherence of the patient to the therapy. The use of orodispersible films has emerged as a way to overcome some drawbacks of conventional methods of drug delivery, especially for patients experiencing difficulty in swallowing. These films are prepared using a matrix that incorporates the drug and contains other substances that confer the properties of the system. The present work describes the use of thermoplastic starch as a carrier for the model drug diclofenac, including film preparation and testing of its orodispersible potential. Preparation of the film employed a microwave oven to gelatinize and plasticize corn starch, with incorporation of the model drug, followed by solvent-casting. The samples were characterized using mechanical tests, analyses of water uptake and water content, and Fourier transform infrared spectroscopy. The results indicated that the film presented promising properties as an alternative system for oral drug administration, with good incorporation and distribution of the drug in the matrix. The material displayed satisfactory mechanical properties, which are crucial for this type of material, due to the need for oral administration and handling before use.

Keywords: Orodispersible film. Thermoplastic starch. Diclofenac.

INTRODUCTION

Orodispersible films are used for the administration of orally absorbable drugs, especially designed for geriatric and pediatric patients with swallowing problems (He *et al*., 2021; Mahboob *et al*., 2016). They have low risk of asphyxiation, ensuring the safety and comfort of the patient (Mahajan, Chhabra, Aggarwal, 2011; Siddiqui, Garg, Sharma, 2011). In addition, the sublingual route provides rapid absorption, due to the highly vascularized mucosa (Adams, 2003).

The excipients used for preparation of orodispersible films consist of the major component, corresponding to the matrix in which the drug (active pharmaceutical ingredient) is loaded, and the substances used to achieve the desired properties of the film, such as malleability, flavor, and solubility, among others (Bala *et al*., 2013; Bisharat *et al*., 2019; Cai, Mesquida, Jones, 2016; Deore, Mahajan, 2018; Hoffmann, Breitenbach, Breitkreutz, 2011; Kathe, Kathpalia, 2017; Nishigaki *et al*., 2012; Ozaltin *et al*., 2019; Sabaa *et al*., 2019; Salamanca *et al*., 2018; Smart, 2005). The matrix is normally based on polymers that may be synthetic or from natural sources. The synthetic polymers most used in the preparation of orodispersible films are poly(vinylpyrrolidone) and poly(ethylene oxide), while the natural polymers include pullulans, starch, gelatin, pectin, sodium alginate, and maltodextrin (Arora, Chakraborty, 2017).

Starch is a hydrophilic natural polymer extensively used in the food industry and as an excipient in pharmaceutical preparations. In the latter case, starch is often used *in natura*, in the form of grains, as extracted from plants. However, for orodispersible films, it must be gelatinized and plasticized, in order to become filmogenic. Gelatinization disrupts the crystalline grain structure of the raw starch, generating an amorphous phase that allows dispersal of the active drug. The plasticizer molecules distribute among the starch

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macromolecules, with this interaction changing the mechanical properties of the material and increasing its malleability (Carvalho, Trovatti 2016; Carvalho, 2008; Shukla *et al.*, 2019). Glycerol and polyethylene glycol are examples of widely used plasticizers (Bala *et al*., 2013; Bisharat *et al*., 2019; Cai, Mesquida, Jones, 2016; Deore, Mahajan, 2018; Hoffmann, Breitenbach, Breitkreutz, 2011; Kathe, Kathpalia, 2017; Nishigaki *et al*., 2012; Ozaltin *et al*., 2019; Sabaa *et al.*, 2019; Salamanca *et al*., 2018; Smart, 2005).

Orodispersible films are commercially available for the delivery of drugs such as benzocaine, phenylephrine-dextromethorphan, and phenylephrine, using the products Chloraseptic®, Triaminic Thin Strips Day Time Cough & Cold®, and Sudafed PE®, respectively, among others. Several of these orodispersible films employ starch as the matrix for drug incorporation, due to its desirable properties, especially solubility in the mouth when used in the form of films.

Diclofenac is one of the drugs suitable for delivery in the form of an orodispersible film, since it is traditionally administered orally, including as orodispersible tablets. Previous work (Khadra *et al*., 2019) reported the preparation of an orodispersible film containing diclofenac, using hydroxypropyl methylcellulose as the polymeric matrix for its incorporation. However, there is a need for further research concerning the development of orodispersible films containing diclofenac, in order to consolidate the preparation process, defining important parameters for the incorporation process and use of the product in the form of a film.

The aim of the present work was to develop an orodispersible film, with plasticized starch as the main excipient component, as a simple and efficient formulation for drug administration. The process employed a microwave oven to prepare the matrix, followed by incorporation of the drug, with heating and drying steps. Diclofenac was used as a model drug. The samples were characterized using mechanical tests, measurements of water uptake and water content, and Fourier transform infrared spectroscopy, in order to evaluate the properties of the system as an alternative for oral drug administration.

MATERIAL AND METHODS

Sodium diclofenac (Sigma-Aldrich), glycerol (Synth), corn starch (food grade, 28 wt% amylase, Maizena® brand), and phosphate-buffered saline solution (PBS, pH 7.2) were used as received.

Film preparation

Starch (8 g) and water (100 g) were mixed at room temperature and heated in a microwave oven (700 W) for 60 s. Glycerol (2 g, corresponding to 20 wt%) was mixed with the warm gelatinized starch, gently homogenized, heated in a microwave oven (700 W) for 30 s, poured into Petri dishes, and dried by solvent-casting for 48 h at room temperature. For preparation of the film loaded with diclofenac, the drug (0.6 g) was dissolved in glycerol (2 g, corresponding to 20 wt%), followed by the same procedure described above. After drying, the samples were cut into appropriate sizes for the tests. The visual appearances of the samples were recorded using an Apple® iPhone X® camera. The dimensions of the films were measured (in triplicate) using a micrometer and a pachymeter (Mitutoyo). The films without and with diclofenac were denoted CF (control film) and DF, respectively.

Water content

The films (with dimensions of 30 × 30 × 0.1 mm) were kept for 48 h at 25 ºC and 50% relative humidity (in an air-conditioned room), followed by weighing. They were then dried at 100 ºC in an oven for 24 h (or until reaching constant mass). The water content was determined as follows:

$$Water\ content = [(W0-Wt)/W0]*100$$

where, $W0$ is the initial weight of the specimen and Wt is the weight after time t.

Water uptake

The water uptake of the films (with dimensions of 25 × 25 × 0.1 mm) was evaluated by immersion in

phosphate-buffered saline (pH 7.0) at 37 ºC. A minimum of three samples were tested for each material, with periodic measurements of the weight increase during 1 h. The samples were removed from the water and the wet surfaces were immediately gently wiped dry, followed by weighing and re-immersion in the water. The water uptake at time *t*, *Wuptake*, was calculated using the equation:

$$Wuptake = [(Wt-W0)/W0]*100$$

where, *W0* is the initial weight of the specimen and *Wt* is the weight after immersion for time *t*.

Contact angle

Contact angle analysis was performed by depositing a water droplet (10 µL) onto the film sample (with dimensions of 3 cm × 0.5 cm × 0.1 cm), followed by measurement using an Apple® iPhone X® camera and FIJI ImageJ® v. 2.0.0-rc-69/1/52p software. Each reported value was the average of five determinations.

Mechanical properties

Mechanical tests were carried out at 25 ºC and 50% RH, using an Instron 5969 Universal Material Testing Machine equipped with a 5 kN load cell, at a deformation rate of 100 mm/s. The sample dimensions were 1 × 9 cm, with thickness of around 100 µm. Six specimens of each film (CF and DF) were tested. Young's modulus was determined as the slope at low strain. The tensile strength and elongation at break were calculated using Bluehill 3 software.

Folding endurance tests were performed manually, in an attempt to simulate handling of the films. The films (with dimensions of 20 × 30 mm) were repeatedly folded at an angle of 180º until breaking, counting the number of repetitions.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were acquired using a PerkinElmer Spectrum 100 FT-IR spectrometer equipped with a zinc selenide crystal ATR accessory, with 16 scans in the range from 650 to 4000 cm^{-1}, at resolution of 4 cm^{-1}. The dried films were used for the FTIR analyses. In the case of the diclofenac release tests, the samples were immersed in phosphate-buffered saline (pH 7.4) for 5 min and dried for 24 h in an oven at 30 ºC.

In vitro disintegration of the films in physiological solution

The films (with dimensions of 30 × 30 × 0.1 mm) were immersed in phosphate-buffered saline (pH 7.0) at 37 ºC for 1 h, with no stirring. Three samples of each film were tested. The samples were removed from the water, the wet surfaces were immediately washed with deionized water, and the samples were then dried in an oven at 30 ºC for ~24 h, until reaching constant mass. The disintegration was determined by loss of mass, as follows:

$$Loss\ of\ mass = (Wt*100)/W0$$

where, *Wt* is the weight of the specimen after immersion time *t*, and *W0* is the initial weight.

RESULTS AND DISCUSSION

The control orodispersible film (CF) was completely transparent (Figure 1(a)), while the film loaded with diclofenac (DF) was quite opaque (Figure 1(b)). Both films were flexible, so they could be handled without damaging their structure. Visually, the appearance of the film loaded with diclofenac was highly homogeneous, suggesting that the drug was well dispersed within the polymeric matrix.

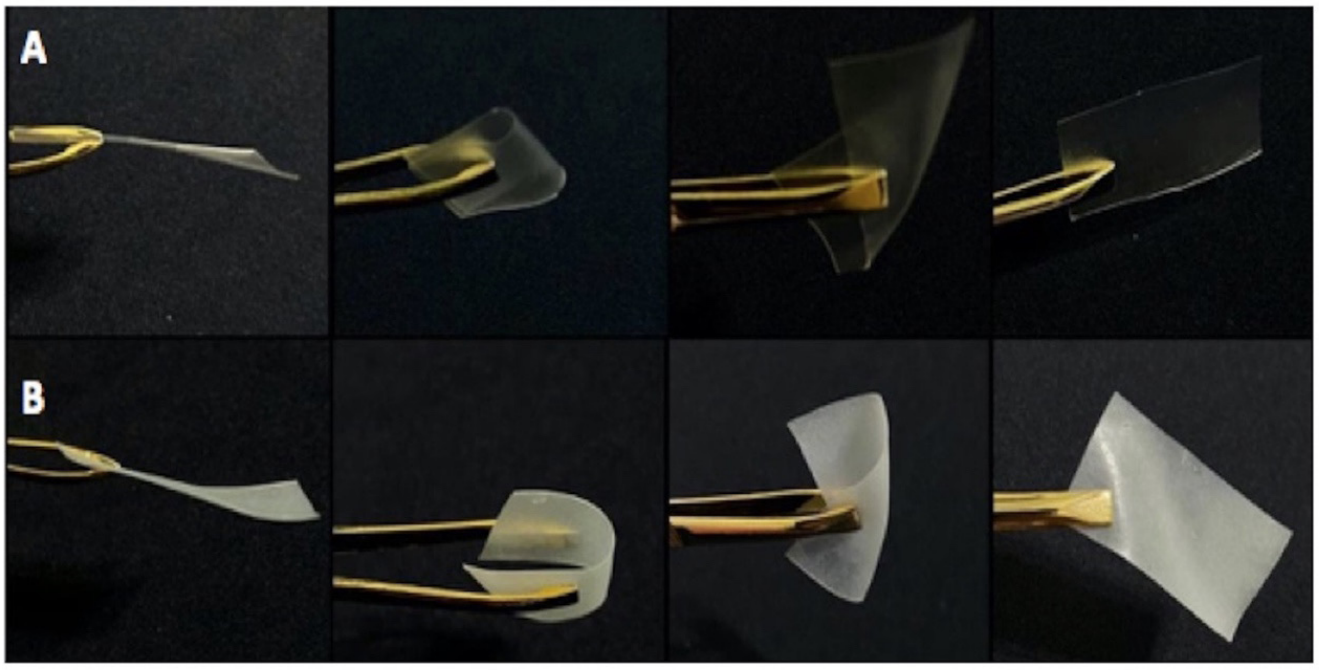

FIGURE 1 - Images of CF (A) and DF (B).

Water content, uptake, and contact angle

The water contents were 16.21 (±0.87) wt% for the control sample and 12.5 (±0.76) wt% for the film containing diclofenac. The lower water content of DF was due to the partial hydrophobicity of diclofenac. A low water content is important for improving sample preservation, so its decrease for DF could be considered a positive feature. These results were similar to those reported for an orodispersible diclofenac film prepared using hydroxypropyl methylcellulose (Khadra *et al.*, 2019), which also had a water content below 20%, complying with criteria to minimize the water available to support microbial growth.

Figure 2 shows the water absorption behaviors of the films. High water absorption was observed during the first 2 min of the experiment, due to the hydrophilic character of the starch. The water absorption rate decreased at about 5-10 min and tended to stabilize after 20 min, reaching 84.47 and 89.49 wt% for CF and DF, respectively, at the end of the experiment. The swelling of the starch film was the first step leading to its disintegration, an essential feature of starch-based orodispersible films for drug administration. It is important to note that saliva increases the disintegration rate, since it is rich in amylase, an enzyme that catalyzes starch hydrolysis. Hence, the results showed disintegration of the film in the presence of water, while the rate of this process would be expected to be higher in a biological system. Figures 2B-E show photographic images of the films before and after the experiment. CF started to break up after the immersion period (Figure 2D), while DF lost its transparency at the end of the experiment (Figure 2E), suggesting the loss of film components.

The contact angles for CF (Figure 2F) and DF (Figure 2G) were quite similar (around 50º), indicating that diclofenac did not affect the hydrophilic character of the film. These results were consistent with the film composition, with starch being the major component, while diclofenac contributed only 3 wt%.

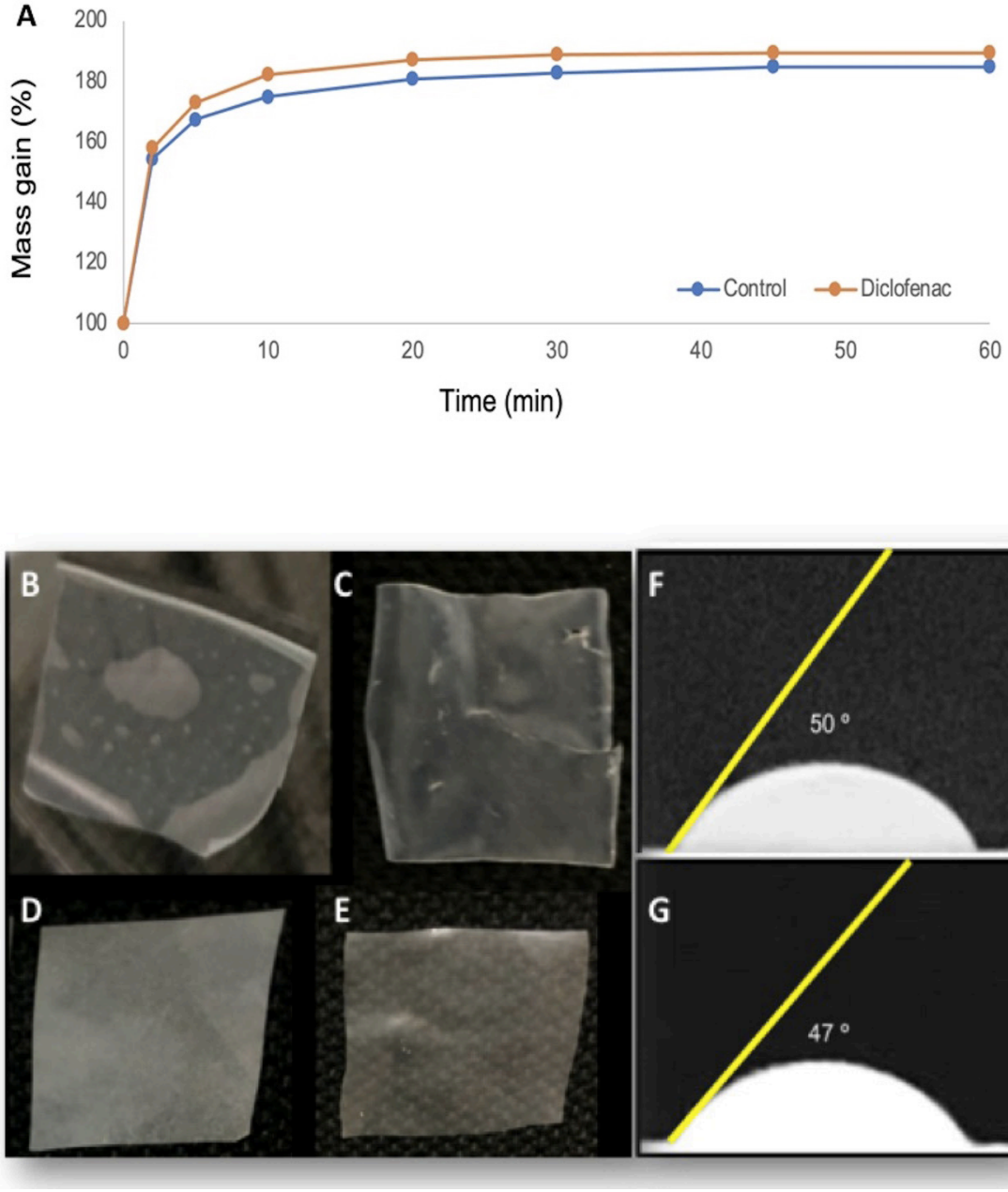

FIGURE 2 - Water uptake curves for CF and DF (A), CF before (B) and after (C) water adsorption, DF before (D) and after (E) water adsorption, and the water contact angles for the control film (F) and the diclofenac-loaded film (G).

Mechanical properties

The mechanical properties of the films were measured using tensile tests. The tensile stress-strain curves are presented in Figure 3. The data for Young's modulus, ultimate tensile strength, and strain-to-failure are presented in Table I. The stress-strain curves showed that both films presented typical stress-strain behavior of plasticized starch. At low strain (around 1%), the curves showed linear elastic behavior, with the elastic

region being followed by a gradual change to a plastic profile, typical of plasticized starch-based materials. The Young's modulus and tensile strength were similar for CF and DF, although the elongation at break was lower for DF. Incorporation of the diclofenac particles in the starch matrix could lead to defects within the starch macromolecules network, consequently decreasing the elongation at break of the DF samples. This is clearly shown by the data in Table I, with similar Young's modulus and tensile strength, but divergent strain-to-failure values.

The mechanical properties of films are crucial for their application as orodispersible matrices for drug release, since they must be introduced into the mouth and accommodated at the palate or under the tongue, without causing irritation or uncomfortable sensations. In addition, they should not break during handling before use.

The endurance tests indicated the ability of the films to resist damage by folding. The images in Figures 3C and 3E show CF and DF before the endurance tests, together with the broken films after folding 294 (±4.10) and 293 (±3.05) times, respectively. The manual folding tests corroborated the mechanical tests, with the results being in agreement with the literature (Khurana, Ahuja, Khar, 2000; Mukherjee, Bharath, 2013; Patel, Prajapati, Patel, 2007).

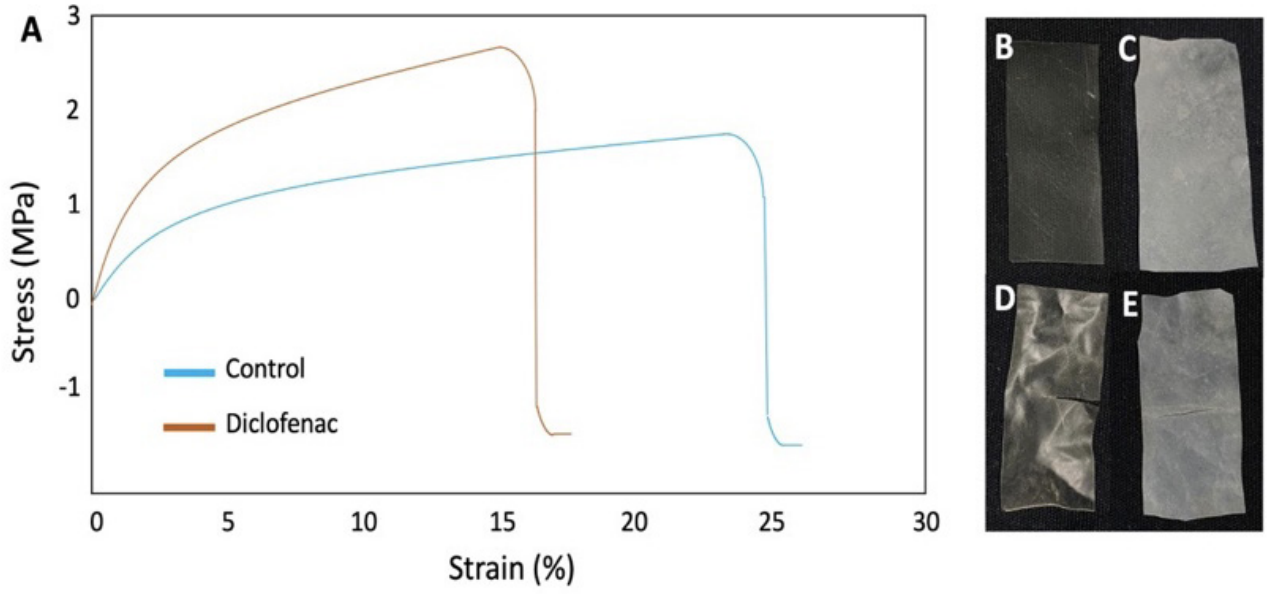

FIGURE 3 - Stress-strain curves of CF and DF (A), and images of the films before (B - CF and D - DF) and after (C - CF and E - DF) the folding endurance tests.

TABLE I - Mechanical properties of the CF and DF films

Sample	Young's modulus (MPa)	Tensile strength (MPa)	Strain-to-failure (%)
CF	71.37 (±2.72)	1.85 (±0.41)	25.15 (±3.24)
DF	73.36 (±2.93)	2.10 (±0.31)	16.22 (±5.97)

Evaluation of the incorporation and release of diclofenac in the starch matrix by FTIR

The FTIR spectra of CF (plasticized starch), diclofenac, and DF are shown in Figure 4. The spectrum of the control film showed peaks at 1000 cm^{-1}, corresponding to CO vibration of the glucose rings, 3300 cm^{-1}, corresponding to vibration of the OH bonds, and 2850 and 2920 cm^{-1}, corresponding to the vibration of CH_2 bonds from the plasticizer (glycerol), in agreement with the literature (Basiak, Lenart, Debeaufort, 2018). The diclofenac spectrum showed bands at 743 cm^{-1}, corresponding to C-Cl vibration of the aromatic ring, 1550 and 1580 cm^{-1}, corresponding to NH vibrations, 2850 and 2920 cm^{-1}, corresponding to CH_2, and 3264 cm^{-1}, corresponding to vibration of NH_2, in accordance with previous work (Ramachandran, Ramukutty, 2014). The spectrum of the diclofenac-loaded film comprised a predominant fingerprint of CF, associated with several peaks from diclofenac, showing perfect overlapping at 743, 1550, 1580, 1460, and 1330 cm^{-1}, reflecting its incorporation into the matrix. The bands did not shift, indicating that the film was an association of its components, with no contribution of chemical interactions among them. The simple mixture of the components, with no strong interactions, could be considered an important property of the orodispersible film, favoring the release of diclofenac from the matrix.

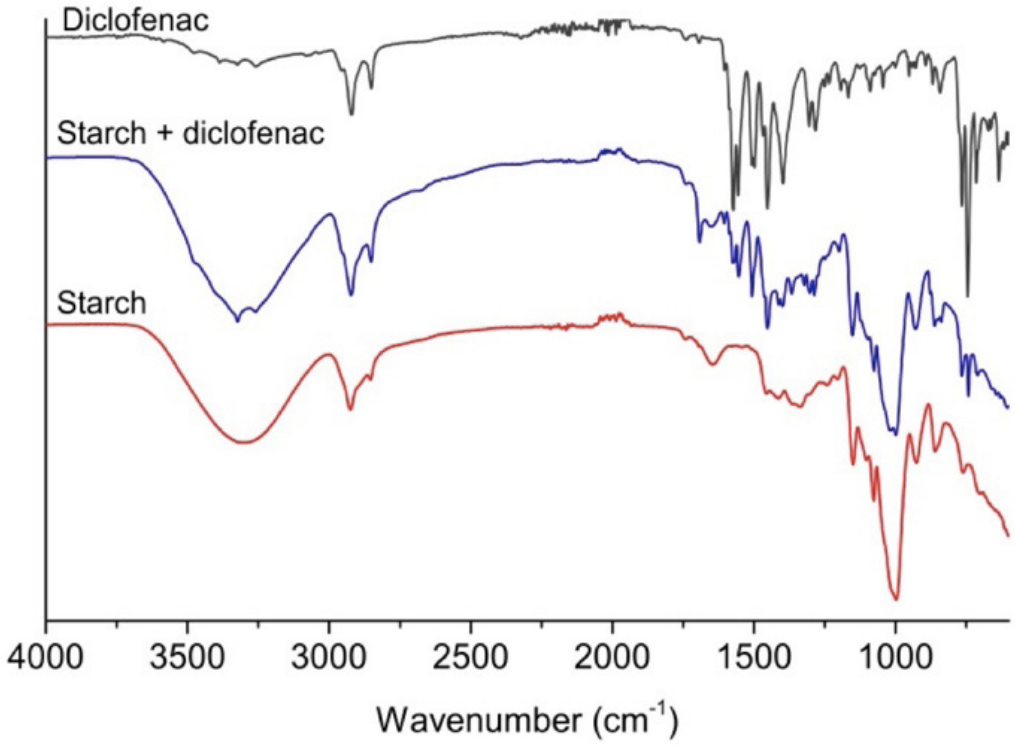

FIGURE 4 - FTIR spectra of diclofenac, CF, and DF.

FTIR was also used to assess the release of diclofenac from the film. Figure 5 shows the spectra of the pure starch film and the diclofenac-loaded film after the release test. The spectra were very similar, with no diclofenac bands appearing after the release test, indicating that the drug had diffused into the liquid medium and was therefore not detected by FTIR. The band at 3300 cm^{-1} in the starch spectrum corresponded to OH vibration of water, indicating that the moisture content was higher than that of the film after the release test. The visual appearance of the films had completely changed at the end of the experiment, with DF becoming transparent,

similar to CF (Figure 1A). This could be explained by dissolution and release of most of the drug from the film, since the films with diclofenac were cloudy-white before the test (Figure 1B).

FTIR was also used to show the release of the drug, because the standard dissolution test was influenced by the nature of the starch. Starch is a highly hydrophilic and water-soluble polysaccharide, which here was present in the form of a thin film. Hence, after several minutes in water, the film started to disintegrate, with the small pieces of film causing the liquid medium to become cloudy, influencing both collection of the sample and the spectrophotometric reading (even after filtration or centrifugation). The drug release profile was expected to be fast (as indicated by the FTIR results), since this orodispersible film would be chewed or just dissolve in the mouth, rapidly releasing all the drug content. Therefore, the FTIR results indicated the promising potential of DF for the administration of diclofenac, a drug for which immediate activity is required.

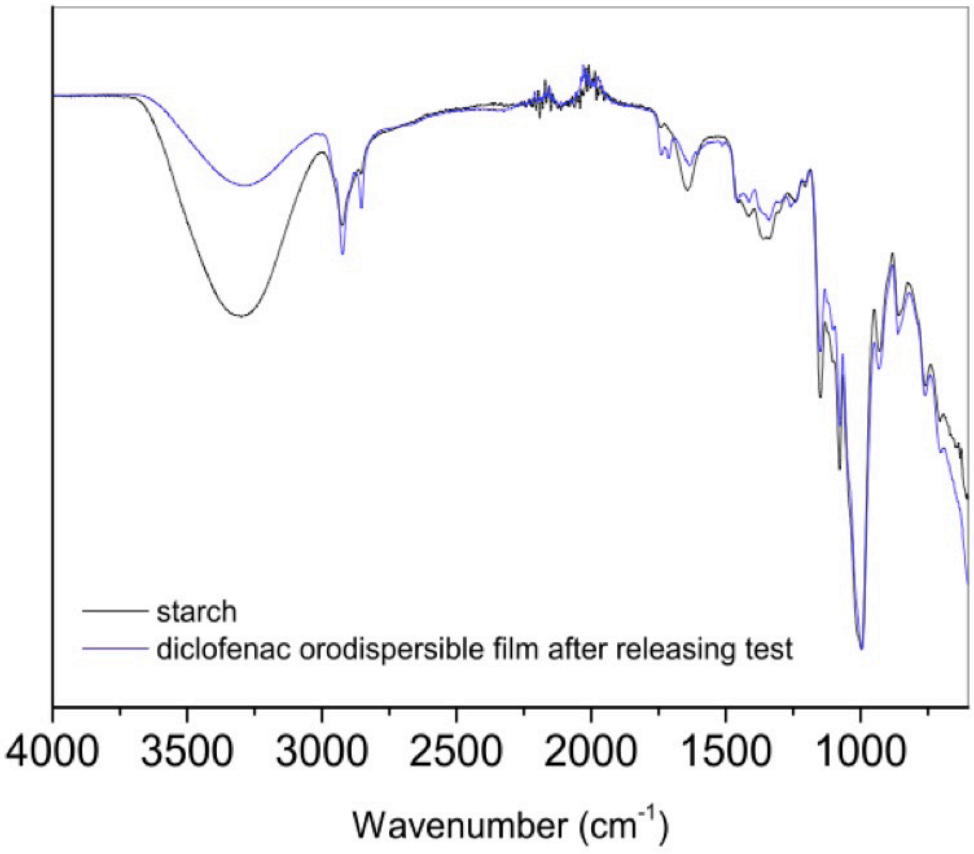

FIGURE 5 - FTIR spectra of pure starch and DF after the release experiment.

Disintegration tests

The disintegration of the samples was confirmed by their mass losses, with CF and DF losing 20.58 and 18.97 wt%, respectively, of the initial mass after the *in vitro* test in phosphate-buffered saline. Figures 6A and 6B show images of CF before and after immersion for 1 h in phosphate-buffered saline, while Figures 6C and 6D show the corresponding images for DF. It can be seen that both films were broken and lost their malleability, indicating the release of glycerol to the medium (since glycerol was the plasticizer). In addition, the diclofenac-loaded film

became transparent, as observed in the release tests. It would be expected that in the mouth, the disintegration would be very rapid, due to the contributions of mechanical friction and the enzymes of the oral mucosa.

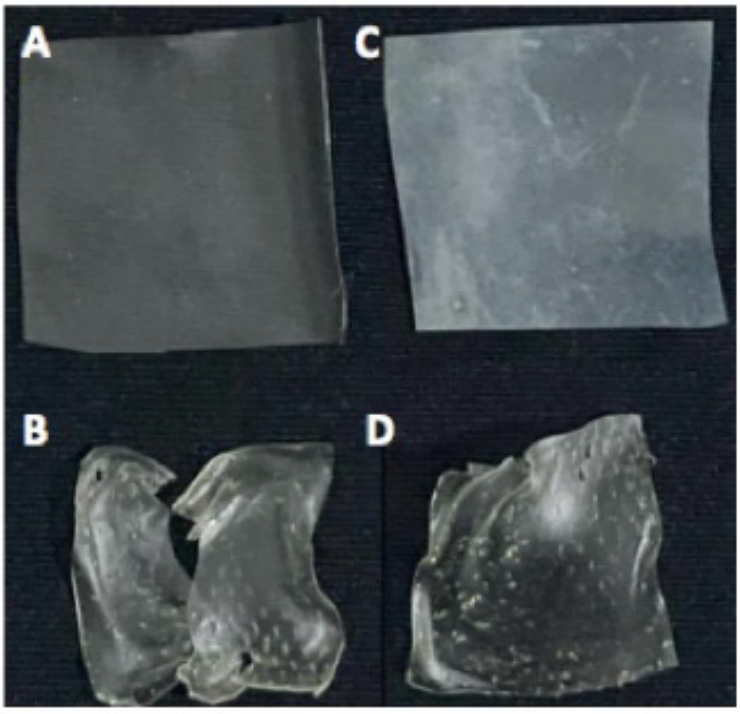

FIGURE 6 - CF before (A) and after (B) the disintegration test, and DF before (C) and after (D) the disintegration test.

In previous work by Khadra *et al.* (2019), the polymeric matrix used to produce diclofenac films was hydroxypropyl methylcellulose, a hydrophilic polymer that dissolves rapidly in the mouth. It was found that these orodispersible films dissolved in less than 1 min, with release of around 80% of the drug (at a dosage of 25 mg) after about 15 min. In the present work, most of the drug was released in less than 5 min, as shown by the FTIR results, in agreement with the earlier findings. The water contents were also similar, at below 20 wt%, which is adequate for avoiding microbial growth. No reports of the mechanical properties of orodispersible diclofenac films were found in the literature. However, the mechanical properties of the thermoplastic starch were in agreement with previous work, where Young's modulus was around 60 MPa and strength at break was around 4-5 MPa (Trovatti, Carvalho, Gandini, 2015). Another study (Senthilkumar, Vijaya, 2015) reported a fast release time of less than 5 min for orodispersible films obtained using starch as the matrix and loaded with etoricoxib, in agreement with the present results. However, very high Young's modulus of around 375 MPa, together with low elongation at break of around 0.7%, indicated that the film was more brittle than the one produced in the present study.

CONCLUSIONS

An orodispersible film loaded with diclofenac was prepared using a simple, inexpensive, and fast method. The film presented attractive features for use as an alternative route for drug administration in patients with difficulty in swallowing. Starch plasticized with glycerol was successfully used as the matrix for loading and releasing the model drug diclofenac, as shown by FTIR analyses. The FTIR results also indicated that the drug was very rapidly released from the wet film, which is a crucial

feature for matrices used for orodispersible films. The water uptake, water content, and contact angle results indicated the hydrophilic character of the films. Mechanical tests showed that incorporation of the drug did not compromise the mechanical properties of the film, which displayed good malleability, an essential feature of this type of material, due to oral administration and the need for handling before use. Overall, the results indicated that the developed film is a promising material for application as the matrix of orodispersible films, with excellent potential for future use in the development of drug formulations.

DECLARATIONS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data presented in this study are available, on request, from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: E.T. and F.T.; Methodology: F.T.; Formal Analysis: E.T. and A.J.F.C.; Investigation: F.T., B.S.M., and C.S.T.A.; Resources: E.T. and A.J.F.C.; Data Curation: E.T. and A.J.F.C.; Writing – Original Draft Preparation: F.T., B.S.M., and C.S.T.A; Writing – Review & Editing: E.T. and A.J.F.C.; Supervision: E.T.; Funding Acquisition: E.T. and A.J.F.C.

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