DEVELOPMENT OF A DRUG RELEASE SYSTEM FOR RHEUMATOID ARTHRITIS TREATMENT

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ABSTRACT

Rheumatoid arthritis is a disease that affects millions of people. Part of the treatment includes drugs that control pain and inflammation, such as ketoprofen. Continuous use of ketoprofen can cause gastric problems in the patient, and in this sense, the use of sustained release systems is very attractive to minimize side effects. Therefore, in the present work, a system consisting of pectin microparticles containing the drug associated with an alginate mucoadhesive film was developed for sustained release. The films presented adequate morphological characteristics and mechanical properties and the release of the drug was probably determined by drug migration to the surface of the films during drying and storage followed by rapid matrix wetting and swelling.

Keywords: Ketoprofen. Sustained Release. Alginate. Pectin.

1 INTRODUCTION

Rheumatoid arthritis is an autoimmune disease that affects around 14 million people worldwide[1]. This disease causes inflammation in the joints, decreased physical mobility and erosion of bone and/or cartilage. One of the medications used during treatment to reduce inflammation and relieve pain is ketoprofen (Keto), frequently administered orally. If used for extended periods, Keto may induce gastric and/or duodenal stress in patients, prompting the development of systems aimed at mitigating these side effects[2]. Drug delivery systems (DDS) are a widely studied alternative for improving drug administration and dosage methods. Characteristics such as biocompatibility and biodegradability of DDS are decisive for their performance and safe use by the patient.

In this work, a mucoadhesive DDS was developed consisting of an alginate film containing pectin microparticles incorporating Keto. This type of DDS can be used, for example, to administer the medication sublingually (under the tongue), to enable the administration of the active ingredient directly through the oral mucosa, minimizing contact with the gastric system and duodenum.

2 MATERIAL & METHODS

Pectin particles were produced using the prilling method[3], by dripping a 6% aqueous solution of the polysaccharide into a crosslinker solution (2% $CaCl_2$) under 100 rpm stirring. For the formulations containing Keto, the drug was added to the pectin solution at a concentration of 28 mg/L.

The films were produced using the casting technique[4,5,6]. A 2% aqueous alginate solution pre-crosslinked with 0.5% $CaCl_2$ was poured onto a polystyrene plate and dried for 48 h at 37 °C. The films were exposed to a second cross-linking step by immersion in a 2% $CaCl_2$ solution and were then washed, dried, and kept in a desiccator with activated silica for at least 24 h.

The particles were characterized in terms of appearance, morphology, and geometric characteristics, by visual inspection and image analysis using the ImageJ software. Films with and without particles were evaluated regarding morphology (by visual inspection and scanning electron microscopy, SEM), thickness, mechanical properties, degree of swelling, and stability related to mass loss in simulated saliva solution (SS). The contact angle of SS on the surface of particle-free films was also determined.

Drug release from the films was analyzed for specimens measuring 2 cm x 2 cm, in triplicate, each containing two microparticles of pectin, with or without (as a control) the drug. Each sample was placed in a vial containing 3 mL of simulated saliva solution. The samples immersed in simulated saliva were maintained at 37 °C under 100 rpm mixing. At predefined intervals, they were subsequently transferred from one vial to the next time point vial containing the same volume of fresh solution at 37 °C. At the end of each analysis time, 1 mL aliquots of the liquid phase were collected and analyzed by spectrophotometry at 260 nm.

3 RESULTS & DISCUSSION

The particles obtained in the presence or absence of the drug showed high sphericity (minimum value of 0.90 ± 0.01). Particles with Keto showed a significantly larger average diameter than those without the drug (2.41 ± 0.18 mm versus 1.80 ± 0.13 mm, respectively). As indicated in Figure 1, the film obtained without particles (Figure 1a) presented a smooth surface, with good transparency and no irregularities. Films containing particles loaded (Figure 1c, d) or not with Keto (Figure 1b) also showed adequate visual aspect, and the presence of the particles dispersed in the film was easily detected.

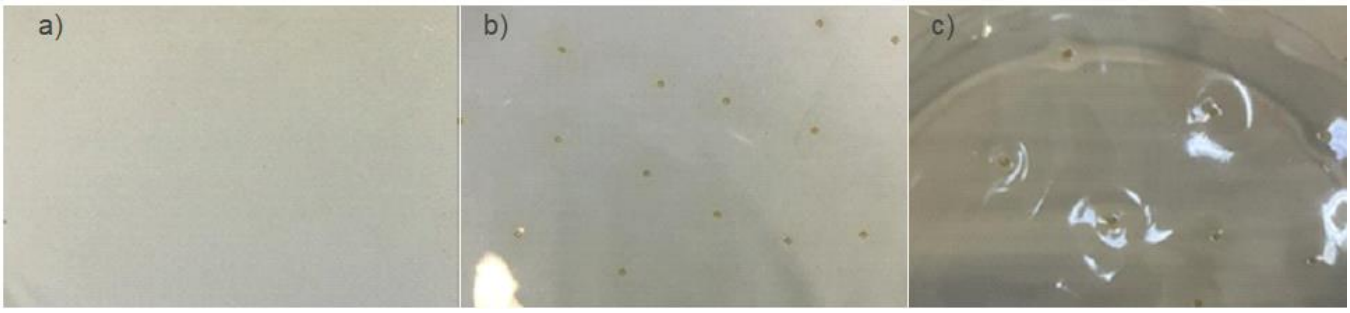

Figure 1 Typical visual aspect of films analyzed by visual inspection: a) Alginate film without particles; b) Film with drug-free particles; c) Film with particles containing Keto.

The results obtained by SEM also indicated smooth surfaces, with almost no roughness, of the films without particles (Figure 2a). The analysis of the cross-section of the same sample indicated that the film is not porous. Tension lines oriented in the direction of the stress applied to fracture the film with liquid nitrogen were observed. Void regions were not identified at the interface nor at the cross sections of the specimens containing particles (Figures 2b-d), which indicates that the technique used to produce the films was sufficient to assure the effective insertion of the particle in a well-positioned manner, also showing good miscibility between the polysaccharides, both for formulations with and without Keto.

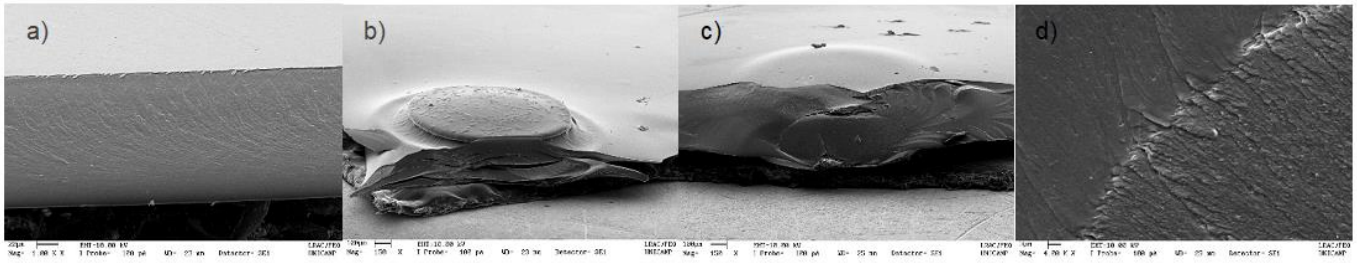

Figure 2 Results of SEM analysis of the films produced: a) without particles (1,000x magnification); b) detailing the interface of a particle not incorporating Keto (150x magnification); c-d) detailing the interface where a particle containing Keto was present (image c with magnification of 150x and image d with magnification of 4,000x).

The results of the thickness, mechanical properties, swelling, and contact angle of the films produced are summarized in Table 1. The thickness of the films in the particle-free region was found to be within the expected range[4,7] and no significant differences were observed in the average thickness of the films in the formulations used (0.11 – 0.13 mm). In the regions of films with particles, the thickness increased significantly. The mechanical properties of the films were close to values already found in the literature[7,8]. The particles containing Keto showed significantly lower stress at break than the others, possibly due to the larger size of the particles containing the drug and to the presence of Keto itself. The elongation at break showed a behavior similar to that of the stress at break, however, no significant differences between the values were observed, possibly due to the greater deviation found for the specimen with ketoprofen. No statistically relevant differences were also found for Young's modulus, suggesting that the presence of particles in the film does not significantly interfere with its rigidity, that is, the resistance to deformation of the material is not seriously impacted by the particles. Due to the presence of particles, the contact angle was only measured for the particle-free formulation. The contact angle found, equal to 57 ± 11°, indicates a hydrophilic material with high wettability. The high standard deviation value obtained for this property was due to the rapid swelling of the film, which within a few seconds already showed a tumescent behavior in the region where the drop was deposited.

Table 1 Results of thickness, mechanical properties, swelling, and contact angle of the produced films.

Formulation		Thickness (mm)	Stress at break (MPa)	Elongation at break (%)	Young's Modulus (GPa)	Contact angle (°)
Particle-free films		$0.11^{a} \pm 0.01$	$48.33^{a} \pm 7.77$	$2.36^{a} \pm 0.61$	$2.25^{a} \pm 0.14$	57 ± 11
Films with particles not containing Keto	Region free of particles Region with particles	$0.13^{a} \pm 0.02$* $0.53^{b} \pm 0.02$**	$55.02^{a} \pm 6.06$	$2.94^{a} \pm 0.73$	$2.46^{a} \pm 0.50$	-
Films with particles loaded with Keto	Region free of particles Region with particles	$0.11^{a} \pm 0.01$* $0.59^{c} \pm 0.02$**	$25.18^{b} \pm 12.11$	$1.86^{a} \pm 1.13$	$1.95^{a} \pm 0.45$	-

* Thickness of region without particles. ** Thickness of region with particles.

As observed in Figure 3, the swelling of the films in the simulated saliva solution occurred quickly, reaching a plateau in just over 10 minutes. The maximum degree of swelling was close to 1 g/g, ranging from 0.882 ± 0.044 to 1.026 ± 0.025 g/g. After long exposure periods to simulated saliva solution, matrix fragmentation was observed.

The drug was released from the system consisting of the film incorporating particles with ketoprofen immediately after exposure to the simulated saliva solution (in up to 1 min). This behavior characterizes burst release and is likely associated with a set of phenomena, beginning with the migration of Keto molecules closer to the surface of the films during drying and storage steps, leading to a heterogeneous distribution of the drug[9]. As a consequence, Keto could probably be more easily released. The rapid matrix wetting and swelling may also have facilitated drug release through Fickian transport. Due to the very rapid release of the drug and its low concentration in the system (which hindered its detection over extended periods), it was not possible to unequivocally determine which was the predominant mechanism responsible for KETO fast release.

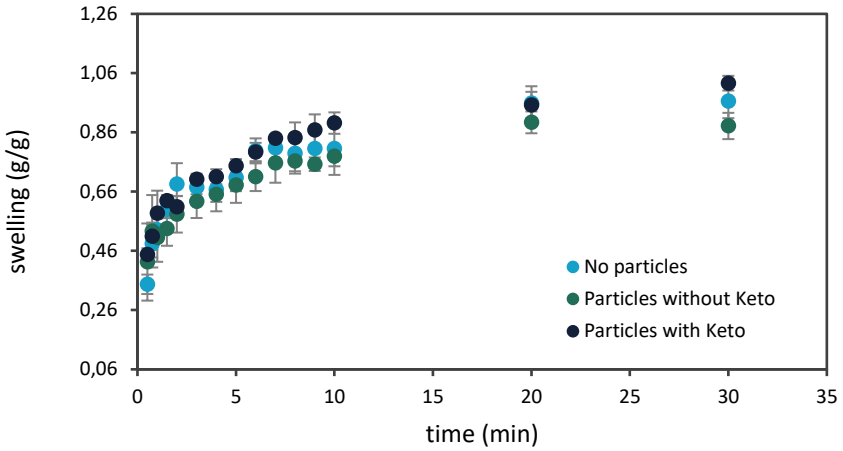

Figure 2 Results of the film swelling test in simulated saliva for up to 30 minutes.

4 CONCLUSION

Pectin and alginate showed good miscibility in the system formulation. The mechanical properties of the films were within those expected for similar formulations reported in the literature. The release of the drug occurred abruptly in the initial seconds. The system used was not effective in controlling Keto release, probably due to heterogeneous accumulation of the drug closer to the film surface during drying and due to the rapid swelling of the matrix, which leached the drug from the system practically instantly. The matrix suffered erosion after long periods, indicating low stability after prolonged immersion in simulated saliva solution. It is recommended that additional crosslinking of both pectin particles and alginate films is tested to increase drug retention in the initial SS exposure period.

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