Controlled Release of Diclofenac by a New System Based on a Cellulosic Substrate and Calcium Alginate

Mohamed Fertah,[a,*] Ahmed Belfkira,[a] Moha Taourirte,[a] and François Brouillette [b]

Promising controlled release systems were prepared from renewable natural products. Paper, used as the system core, was made with commercial kraft pulp and with bleached lignocellulosic pulps extracted from local plants. The characteristics of those pulps (fines content and fiber length) as well as paper thickness, porosity, and roughness, were evaluated. Alginate served as the protective membrane. The releasability of Diclofenac as a function of time and pH was studied under constant temperature (37 °C) and constant stirring (200 rpm). Also the influence of the type of paper and the calcium alginate concentration in the protective layer were highlighted. The extent of release reached 80% in a basic medium in a variable time interval 7 to 16 h, whereas in an acid medium it did not exceed 24% in 33 h. Diffusion, Fickian diffusion, and diffusion-erosion were judged to be important contributing mechanisms based on the Korsmeyer-Peppas kinetic model for those various matrixes. Different formulations were found to have significant controlled release properties that could be used in the prolonged release of the active ingredients. Because of the low release in acidic medium, the formulated system could be a good candidate to protect the active ingredient from acidic medium.

Keywords: Controlled release matrix; Cellulosic substrate; Alginate; Kinetic models; Diclofenac

*Contact information: a:Laboratory of Bioorganic and Macromolecular Chemistry (LBMC), CadiAyyad University, Faculty of Sciences and Technology, Av.Abdelkarim Elkhattabi, BP 549, Marrakesh, Morocco; b: Lignocellulosic Materials Research Centre (CRML), Université du Québec à Trois-Rivières, Box 500, Trois-Rivières,QC,G9A 5H7, Canada; *Corresponding author: fertmoh@yahoo.fr*

INTRODUCTION

The controlled release (CR) of biologically active molecules is a strategic research axis in the life sciences and materials science sectors as well as on the fundamental level such as in medical applications areas. The metabolic and environmental fate of active substances (drugs, pesticides, aroma, *etc*.), and excipient has been a subject of interest since the appearance of CR systems. Many of these systems are based on polymers that have chemical structures that undergo little or no change once they are released into the environment, as in the case of the polymethyl methacrylate (Bettencourt and Almeida 2012; Doerdelmann *et al.* 2014). In these last few decades, several research groups around the world have been studying the development of CR systems based on natural macromolecules.

The first CR matrix using carboxylic/quinine resins was described by Saunders and Srivastava (1950). Then, Chaudhry and Saunders (1956) studied the combination of different types of resins with ephedrine. In the late 1950s, other matrixes, *i.e*., inert lipid and hydrophilic matrixes were discovered (Igor and Mattiasson 2008). Today, research efforts are primarily focused on biodegradable polymers (Manjanna *et al*. 2009). They are cheaper, easy to maneuver, and, importantly, non-toxic and biodegradable. Their

biocompatibility—the capacity of liberation of the hydro-soluble compounds and the ability to modulate their physico-chemical properties—allows the generation of new biomaterials for biomedical and environmental applications. The most widely used and studied are cellulose and starch derivatives, alginates, and polylactides. However, hydrophilic polysaccharide polymers are currently being used for the CR of active ingredients (AI). For example, cross-linked amylase was introduced in the early 1990s as an excipient for the formulation of swellable matrixes for controlled drug release. In recent years, several studies have been devoted to the use of the cellulose derivative, hydroxypropylmethylcellulose. It has been used in tablets to release various AIs (Hogan 1989; Hardy *et al*. 2006; Genç and Jalvand 2008) by means of a ketorolac tromethamine probe. Paracetamol/high amylose was studied by Brouillet *et al*. (2008), and Boudendouna (2010) studied the formulation methodology of the CR dosage forms of Diclofenac/ hydroxypropylmethyl cellulose. Maiti *et al*. (2012) studied the CR of encapsulated Diclofenac that was composed of sodium alginate/starch. In addition, Manjanna *et al*. (2009) studied the various combinations of sodium alginate, chitosan, and hydroxypropyl methylcellulose. Lastly, Novac *et al*. (2009) studied the CR of ciprofloxacin from polyionic complex alginate and chitosan at various pH levels.

The release of ciprofloxacin by a solid biodegradable implant made of cross-linked high amylose starch has been previously studied (Désévaux *et al*. 2002). The implant was found to be biocompatible and bioresorbable. It can be used as an antimicrobial delivery system for the local prevention or treatment of osteomyelitis. Moreover, these systems avoid the need for additional surgery to remove the implant.

The novelty of this work is in the use of the lignocellulosic fiber as paper to contain the desired amount of the AI without getting lost in the calculation of the encapsulation rate in other systems (micro- and nano-spheres). This study attempted to combine the advantages of using paper in an active packaging system with the gelling properties of alginate to create a new system that could be useful in the drug delivery system field.

Most of the research on native or chemically modified lignocellulosic fibers is focused on paper and board production, composite materials, and little in the medical field. This work presents a new use for unmodified lignocellulosic matter. It is well known that paper is made up of a network of fibers interconnected mainly by hydrogen bonds. This network of fibers traps bioactive molecules and releases them at a later time, depending on the density of the network, the nature of the AI, and the coating applied to the fibrous network. Several reasons justify considering such a possibility: (i) the matrix is composed mainly of natural fibers, (ii) it is made from renewable materials, (iii) it is nontoxic, (iv) it is a mastered technology, and (v) it is an economical process. The implementation is also simple and attractive because it only requires paper, an AI, and a coating system with a film playing the role of a semi-permeable membrane able to be disintegrated over time.

In this study the sodium salt of Diclofenac, a non-steroidal, anti-inflammatory drug used in the treatment of rheumatic disorders, was chosen as the probe. This drug is very interesting in oral dosage forms with CR, particularly because of its relatively short biological half-life; therefore, this increases the risk of adverse gastrointestinal complications from the chronic nature of the treatment. The selected coating was sodium alginate, a natural linear and poly-anionic polysaccharide. It refers to all polysaccharides belonging to the family of copolymers consisting of residues of D-mannuronic (M) and L-guluronic (G) acids in different proportions and sequential arrangements (Fig. 1).

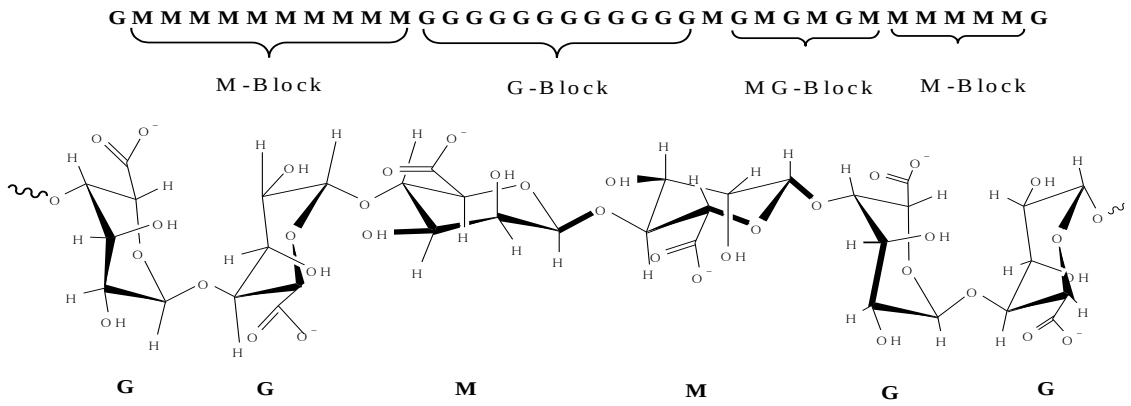

Fig. 1. Structure of the alginate (Igor and Mattiasson 2008)

Alginate has the property of crosslinking, especially *via* guluronic acid, which can be linked to a similar functional group in another alginate molecule by a Ca^{2+}cation or another multivalent cation. In the pharmaceutical industry, alginate is used as an excipient for drug formulation or as a protective membrane for the AI in the microencapsulation process (Insel 1998).

Our objective is to promote the trapping of Diclofenac (the AI) by the lignocellulosic fiber network for its CR. The determination of factors influencing the dissolution of the AI encapsulated in such a form is important. Potentially, various factors will influence the release of Diclofenac: (i) the solubility of the AI in the release medium and the polymeric wall, (ii) the encapsulation rate, (iii) other interactions such as AI/fiber, AI/alginate, AI/Ca^{2+}, fiber/alginate, and fiber/alginate/Ca^{2+} (iv) the characteristics of the entire network (porosity, tortuosity, surface, shape, *etc.*), and (v) the characteristics of alginate, such as the molecular weight marker (Igor and Mattiasson 2008).

EXPERIMENTAL

Paper

Different pulp blends were used for the preparation of fibrous substrates. They were composed of softwood bleached kraft market pulp as a default pulp and pulps obtained from six Moroccan plants: dis grass (*Ampelodesmos mauritanicus*), distaff (*Typha latifolia*), rush (*Juncus effusus*), halfa or alfa (*Stipa tenacissima*), pennisetum *(Pennisetum alopecuroides*), and agave (*Agave americana*). These were harvested from the province of Kelaa Sraghna located in the Marrakech Tensift-El Haouz region. Paper sheets were produced and characterized according the C5 and D12 PAPTAC standard methods (1993, 2003). Table 1 contains characterizations performed on all samples. Scanning electron microscopy (SEM) images were also acquired to characterize the surface and the degree of entanglement of the samples.

Plant samples were soxhlet extracted with a 2:1 toluene/ethanol blend for 8 h to eliminate lipidic and phenolic substances. Then two treatments were performed to extract hemicelluloses and lignin: soaking in a 2 wt. % NaOH solution and in a 2 wt. % blend of NaOH and hydrogen peroxide (Vassilev *et al*. 2010).

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Table 1. Properties of Paper Samples

Paper Source	Thickness (µm)	Porosity (mL/min)	Roughness (µm)	Fines content (%)	Basis weight (g/m^2)	Specific volume (cm^3/g)
Kraft	142	2292	9.10	24.00	81.53	1.74
Diss	117	163.33	12.29	60.06	77 .57	1.51
Typha	107	228.33	6.88	54.26	76.44	1.40
Halfa	129	2140	9.50	42.61	74.74	1.73
Pennisetum	98	87.67	7.19	57.05	82.66	1.19
Agave	99	2.67	10.81	55.63	77.56	1.28
Rush	107	1161	7.98	38.57	77.57	1.38

Protective Membrane: Alginate

Sodium alginate was extracted from brown algae, *Laminaria digitata*, that was collected from the coast of El Jadida, Morocco. Fertah *et al*. (2014) studied the extraction of alginate in a previous work and determined that the intrinsic viscosity was 2.542 dL/g, which was calculated by measuring the viscosity of the diluted solutions. The Mark-Howink equation (Orive *et al*. 2002) was used to calculate the viscosimetric average molecular weight of 1.19 10^5 g/mol. The spectroscopic measurements, infrared and Hydrogen-1 Nuclear Magnetic Resonance (H^1NMR), were used to determine the mannuronic fraction/guluronic fraction (M/G ratio) (Smidsrød and Draget 1996). This index provided important information about the nature of the gel formed from the alginate.

Active Ingredient:Diclofenac

Diclofenac,2-[2-(2,6-dichlorophenyl) aminophenyl] ethanoic acid, was the AI used in the experiment (Fig. 2). It has analgesic, antipyretic, and anti-inflammatory properties, and is an inhibitor of cyclo-oxygenase. Diclofenac is known to reduce the intracellular concentrations of free arachidonate in leukocytes, perhaps by altering the release or re-uptake of fatty acids (Insel 1998).The product used in this study was an injectable solution of Diclofenac (as its sodium salt) containing 75 mg of AI in 3 mL of water. The half-life in plasma of unmodified Diclofenac is around 1 to 2 hours (Nayak *et al*. 2010).

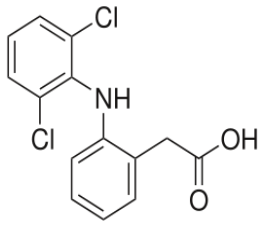


Fig. 2. Structure of 2-[2-(2,6-dichlorophenyl) aminophenyl] ethanoic acid (Diclofenac)

Preparation of Matrixes

Matrixes were composed of three major components: paper (lignocellulosic fibers network), the sodium salt of Diclofenac (AI), and calcium alginate (protective membrane). A well-defined paper surface (1.8 x 1.8 cm^2) was soaked in a fixed volume (0.2 mL) of a solution of known concentration of AI (75 mg/ 3 mL). After drying, a solid calcium alginate

shell was formed by adding a solution of calcium chloride (1%) on a gel of sodium alginate layer deposited on the entire sample.

Instrumentation

The release of Diclofenac was evaluated in a custom laboratory release device. The system was composed of a 200 mL container, a magnetic stirrer set at 100 rpm, a temperature regulator (37±1 °C), a pH meter, and a sample carrier. The carrier was an aluminum mesh specifically selected to ensure that swelling could occur in three dimensions with the penetration of water from all sides of the matrix. The dosage of the CR of AI was performed using dual beam Specord 210 Plus spectrophotometer UV–visible from Analytic Jena (Germany), covering the wavelength range from 190 to 1100 nm, with quartz cells thickness of 0.2 cm. The samples were analyzed at a wavelength of 276 nm.

Methods

To obtain different protective membranes, papers were encapsulated with three different thicknesses of the protective membrane (e1, e2, and e3, where e1 < e2 < e3). A stock solution of alginate (200 mg/10 mL) was prepared, and each membrane was formed by adding 1, 5, and 6 mL of the stock solution to the paper, respectively (Fig. 4). For each sample series, the effect of the pH on the release medium (pH = 8.6 and 2.5) and the release profile was investigated. Release media were physiologically buffered media. The release extent of Diclofenac salt in the medium was determined using a calibration curve. Figure 3 illustrates the different components of this system (drug dropped in the paper substrate and encapsulated with calcium alginate).

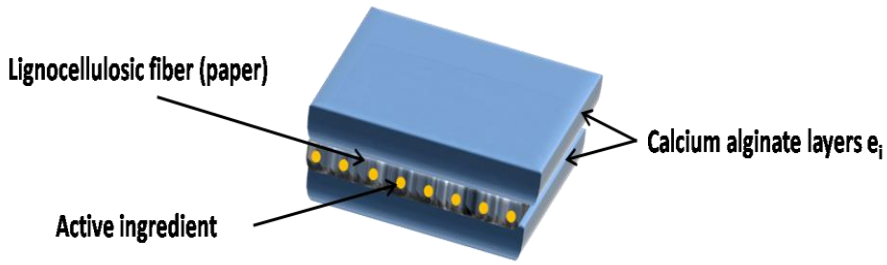


Fig. 3. Illustration of a cross-section of the release system

RESULTS AND DISCUSSION

Matrix Microstructure

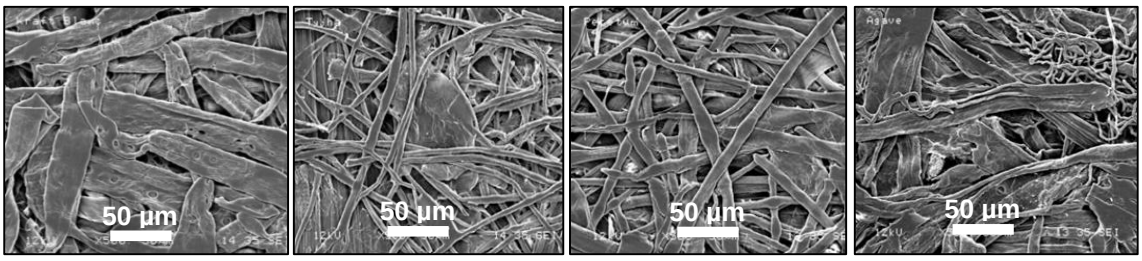
Paper microstructure

The AI was trapped in the paper support matrix, composed of bleached and refined lignocellulosic fibers. The SEM images of the paper samples provide a visual of the entanglement state, the network porosity, and damage that had occurred to the fibers during the different refining cycles, as shown in Fig. 4.

Alginate microstructure

The physical properties of alginate were largely determined by the relative amounts of the three types of blocks in the copolymer, the M/G ratio, and the abundance of G blocks (Davis *et al*. 2003, 2004). The chemical composition of the alginate used in this study was

previously reported by Fertah *et al*. (2014). Divalent Ca^{2+} cations preferentially formed bridges with the G blocks rather than with the M blocks. An "egg box" was regarded as a general model to describe the gel formation (Grant *et al*. 1973; Braccini and Perez 2001). Penman and Sanderson (1972) obtained brittle gels from alginates having a low M/G ratio, and more elastic gels resulted from alginates with an M/G ratio that was greater than 1. Based on these results it was concluded that the alginate had formed soft and elastic gels (Table 2).



(a) Kraft pulp (b) Typha (c) Pennisetum (d) Agave

Fig. 4. Scanning electron micrographs of paper samples elaborated with different pulps (500x)

Table 2. Proportion of Different Sequences in Alginate

F_G	F_M	M/G	F_{MM}	F_{GG}	F_{GM}	F_{MG}
0.47	0.53	1.12	0.47	0.41	0.06	0.06

Alginate from the Moroccan coast has a high amount of both homopolymeric segments: mannuronic fraction (F_{MM}) and guluronic fraction (F_{GG}). Alternate fraction blocks' (F_{MG} and F_{GM}) values were lower than those previously described in the literature by Smidsrød and Draget (1996) and Zheng *et al*. (1994). The SEM image (Fig. 5) illustrated the surface of the sodium alginate film. Gelation by Ca^{2+} created bridges between the different chains of the alginate.

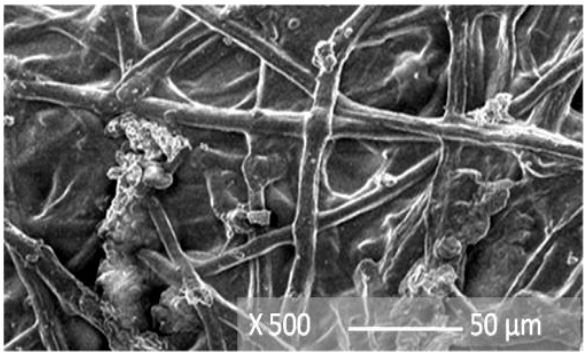


Fig. 5. SEM image of calcium alginate

Diclofenac Release Kinetics

The release kinetics of each matrix: Diclofenac with only alginate and Diclofenac soaked in papers and coated with different amounts of alginate, were analyzed based on: (i) the nature of the fibers constituting the fibrous network, (ii) the amount of alginate that coated the papers, and (iii) the pH of the release medium. Kinetic models were tested to determine the release mechanism of each matrix. The CR system was simply a fibrous network (paper) surrounded by a protective layer that was composed of polyanionic

alginate, complexed with Ca^{2+}. The AI was found in both the fibrous network and the calcium alginate layer.

Release from alginate alone

Since the calcium-form alginate was more soluble in a basic medium than an acidic medium, the release mechanism of the AI was studied at two pH levels: 2.5 and 8. Figure 6 represents the amount of AI released in basic and acidic conditions.

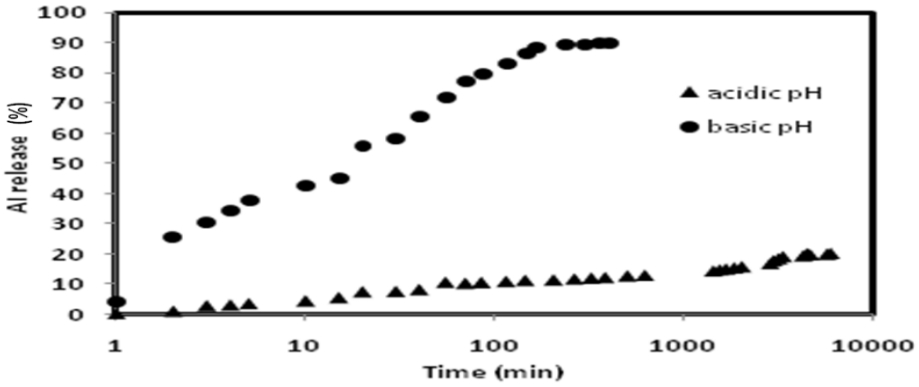


Fig. 6. Release of Diclofenac with an alginate matrix in basic and acidic pH

The initial release of the AI was very rapid. This effect was attributed to the presence of a significant amount of the AI at the surface of the protective membrane and/or the migration of the AI by osmosis through the fibrous network to the alginate gel during its deposition. The evolution of the release was strongly dependent on the medium's pH. As shown in Fig. 6, the release of Diclofenac in a basic environment was much faster than in an acidic environment, because calcium alginate is more soluble in a basic medium. The amount released reached 60% after 40 min and 80% after 2 h. In addition, the release was easier in a basic medium because of the swelling and thinning of the cell wall by an erosion mechanism. However, in an acidic medium, the insoluble matrix containing the AI remained unchanged throughout the duration of the experiment. The only change was in the appearance, because of a slight swelling of the alginate. The release extent over time was much lower, with only a 20% release extent in 4 days.

Release from the kraft fibers/alginate system

The effect of fiber networks, in terms of microstructure, on the retention of the AI was investigated by studying the release kinetics for different alginate protective membranes (e_i) and pH values (Table 3).

Table 3. Time Required to Release 60% of the Diclofenac at Different pH Values and Alginate Layer Membranes

	Time Required to Release 60% of Diclofenac(min)		
Membrane thickness	e_1	e_2	e_3
pH 2.5*	-	-	-
pH 6	145	175	295
pH 8	15	70	85
*the maximum amount released after 72 h varied from 10.6 (e_3) to 23.5% (e_1)			

For the same fiber network, the effect of the concentration of alginate in the deposited layer and the pH was obvious. As noted above, the change in the release profile was different depending on whether the medium was acidic or basic. The dissolution of the calcium alginate in a basic medium caused thinning of the protective layer. Consequentially, the release of the AI was more rapid over time (Table 3; Fig.7).

The increase in thickness of the membrane and the decrease in pH (more acidic) resulted in a decrease in the percentage of the AI released over time (Fig. 7a, b; Table 3). In a highly acidic medium (pH=2.5), the release of the AI was slow (approximately 20%) for the thin alginate layer thickness (Fig. 7c; Table 3).

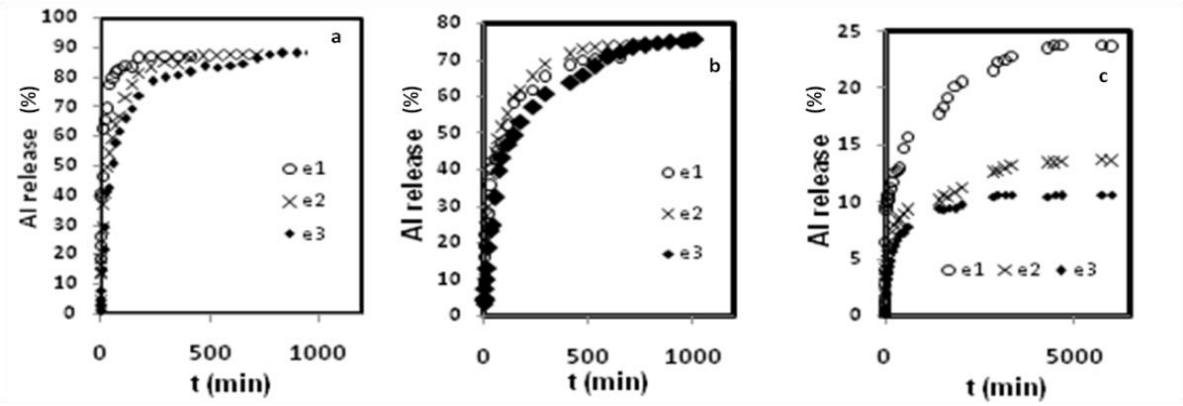


Fig. 7. The effect of the membrane thickness (e_i) of the alginate layer on AI release at a pH of a) 8, b) 6, and c) 2.5

In a more acidic medium (pH=2.5), the alginate layer was insoluble, and therefore the matrix was stable and did not decay (Fig. 7c). Diclofenac, which was less soluble in an acidic medium, was hardly released from the matrix. In addition to its insolubility, hydrogen bonding may have been established between polar regions of the alginate, including carboxyl and hydroxyl groups. Therefore, the amount of AI released decreased as the thickness of the barrier increased. This explains the retention of the AI and the obtained release profiles (Fig. 7c).

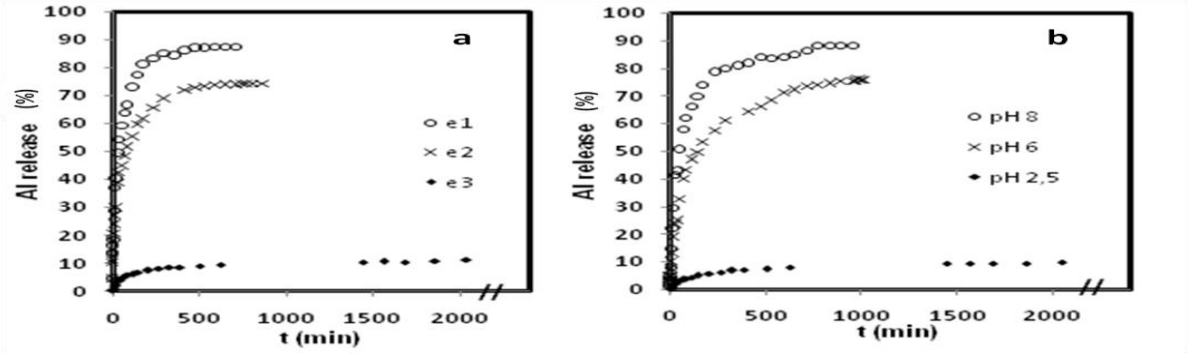


Fig. 8. The release extent of Diclofenac as a function of a) the alginate membrane thickness (e_i) and b) pH

The final percentage of released AI was notably lower than in the basic medium, and the appearance of the matrix remained unchanged, except for slight swelling. Therefore, by varying the alginate concentration and the pH, the profiles for the amount of AI released can be controlled (Fig. 8).

Release from the Moroccan fibers/alginate system

The same release tests were conducted on matrixes made from paper composed of lignocellulosic fibers obtained from plants growing in Morocco. The fibrous networks prepared from six plants differed in terms of their structure, weighted average fiber length, surface energy, and density of the network (Table 1). As shown in Fig. 9, these differences have implications on the AI release kinetics. Indeed, even using the same amount of alginate to coat the fiber network and AI (5 mg), resulted indifferent release profiles. The plots in Fig. 11 are similar to those obtained with paper made of kraft fibers and alginate. The release was rapid, particularly in the case of the basic medium. Again, in an acidic medium, the extent of release was significantly reduced in effect and increased in duration.

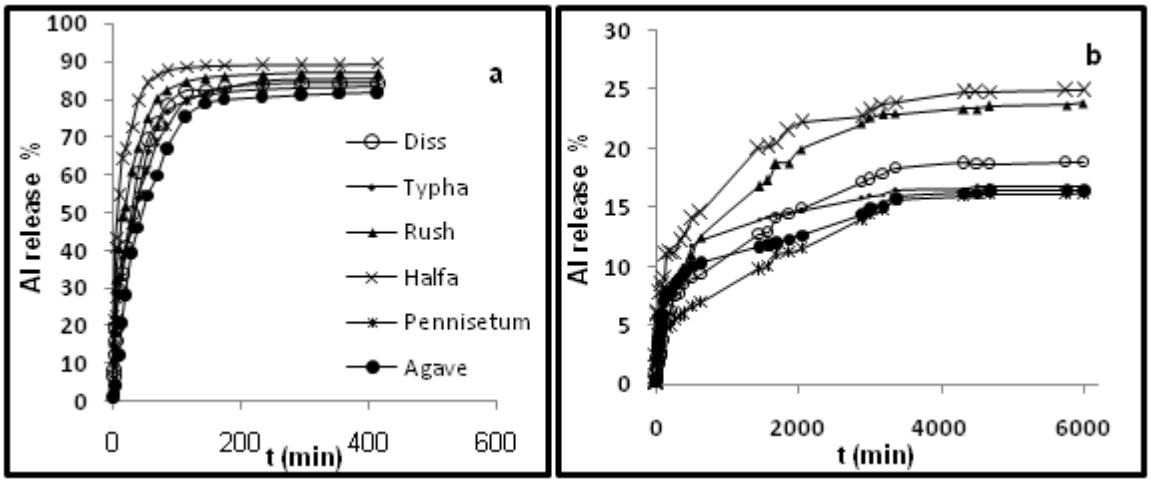


Fig. 9. Diclofenac release extent from Moroccan fibers/alginate matrixes over time (min) for a) pH=8 and b) pH= 2.5

As shown in Fig. 9, the AI release extent differed from one matrix to another. To elucidate this behavior, a composition and the microstructure of fiber networks was examined. There was a parallel evolution between the porosity and the AI release extent (Table 1; Fig. 9a,b).The halfa/alginate matrix, which had the highest specific volume, exhibited the highest release extent. The opposite was observed for the pennisetum/alginate matrix. This matrix had the lowest release extent. However, some discrepancies for this release extent/porosity relationship were observed (Fig. 11; Table 1).For example, the dis grass paper exhibited a higher specific volume (1.51) than the Rush paper (1.38); however, the former had a lower release extent.

By using the composition of the paper, particularly its fines content (which played an important role in the mechanical properties of the system), the phenomenon can be explained by the consolidation of the fibrous network, which occurs because of the links and interactions between the fine particles that are dispersed among the larger fibers. In paper options, the fines contents were 60.02% and 38.57%, respectively. Also, their presence allowed for the retention of the AI molecules. The results indicated that papers formed by conformable, soft, and flexible fibers (containing a higher percentage of fines) would prevent the release of the AI to a greater extent, because of these interactions and the lower porosity.

Diclofenac release mechanisms

Figure 10 shows a schematic for the evolution of the shape of the matrix according to the pH of the medium. Upon introduction of the matrix into the release medium, the hydrophilic alginate hydrated rapidly and released the molecules on the surface ("burst effect"). The presence of the AI in the protective wall (alginate) occurred because of the migratory osmosis effect of the AI from the fiber network to the alginate gel during its deposition on paper. After this first step, the matrix evolved, depending on the pH of the medium. In an alkaline medium, calcium alginate formed a loosely packed layer.

The macromolecular chains became hydrated, and each one occupied a high hydrodynamic volume. The space between the wall constituents had a significant effect on the releasability of the AI. When this space was high, more release was manifested. The phenomenon of release paralleled the erosion of the membrane wall. In an acidic medium, carboxylic acid functions of both the AI and alginate are protonated. Hydrogen bonds will create bridges between the four partners of the matrix: Ca^{2+}, hydroxyls of lignocellulosic fibers, hydroxyl of carboxylate and those of the AI. Consequently, calcium alginate will be relatively insoluble and the matrix underwent only a slight change in appearance. After a "burst effect", the AI was released more slowly. However, in a basic medium, both carboxylate ions of alginate chains and those of the AI were in the form of ions and consequently the solubility increased. In addition, the AI pKa is 4.16, and it will be more soluble in environments with pH>5. This is why, in a basic medium, the AI will be deprotonated and therefore soluble in water. This is what explains the high releasability and the degradation of the membrane.

The CR time was governed by many factors, such as reduced porosity, low AI solubility, and the strong interactions made by the AI and the lignocellulosic fiber. The duration and the kinetics of the release mechanism were influenced by the pH, concentration of the alginate layer, and the nature of the fiber network.

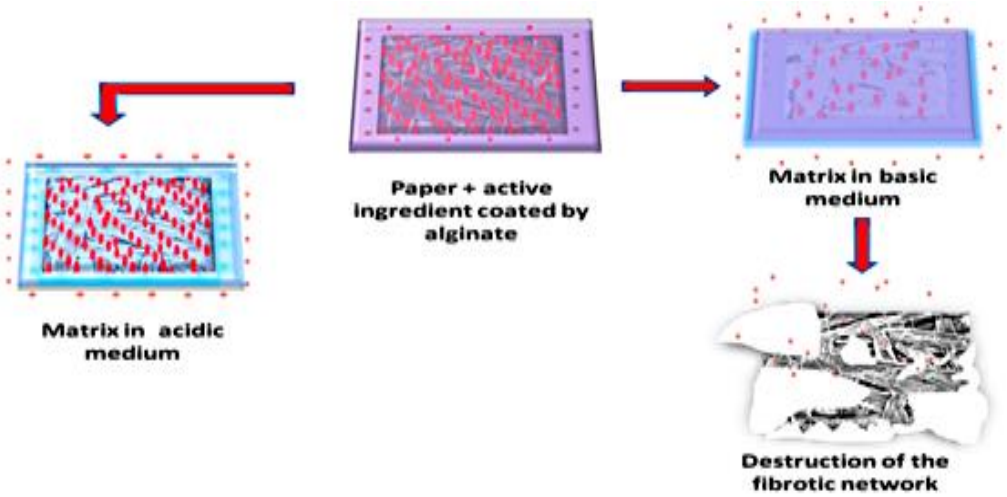


Fig. 10. The release mechanism in a basic and in an acidic medium

To determine the release mechanism of Diclofenac from matrixes examined in this study, models representing the most relevancy were employed: zero order (Najib and Suleiman 1985), first order (Desai *et al*. 1966), the Higuchi model (Higuchi 1963), and the Korsmeyer-Peppas model (Eq. 1) (Korsmeyer *et al*. 1983),

$$\frac{m_t}{m_\infty} = kt^n \quad (1)$$

where, m_t and m_∞ are the quantities released at time t and infinite time, respectively, k is a kinetic constant including the geometrical characteristics of the matrix, t is the time, and n is a constant related to the release mechanism of the AI. The Korsmeyer-Peppas model is valid only for release extents below 60%. The plot of $\ln(m_t/m_\infty)$ versus $\ln(k) + n\ln(t)$ was used to determine n and consequently the release mechanism of the AI.

The choice of an appropriate model to describe the mechanism of release of the AI by the matrixes was selected based on the coefficient of determination (R^2) (Table 4).

Table 4. Linear Regression Coefficients of Determination (R^2) for the Different Kinetic Models

	Zero order	First order	Korsmeyer-Peppas	Higuchi
Kraft paper with membrane e3				
Kraft pH=8	0.618	0.343	0.850	0.717
Kraft pH=6	0.771	0.531	0.957	0.765
Kraft pH=2.5	0.638	0.333	0.803	0.135
Kraft paper with membrane e2				
Kraft pH=8	0.595	0.394	0.893	-0.185
Kraft pH=6	0.675	0.449	0.908	-0.477
Kraft pH=2.5	0.695	0.350	0.872	-0.466
Kraft paper with membrane e1				
Kraft pH=8	0.448	0.351	0.868	-3.066
Kraft pH=6	0.686	0.445	0.925	0.044
Kraft pH=2.5	0.693	0.298	0.812	-0.023
Moroccan Fibers pH=8				
Dis grass	0.552	0.411	0.923	0.392
Typha	0.607	0.447	0.930	0.117
Rush	0.509	0.385	0.900	-0.587
Halfa	0.405	0.317	0.840	-3.791
Pennisetum	0.648	0.473	0.935	0.127
Agave	0.660	0.415	0.920	0.756
Fiber pH=2.5				
Diss	0.804	0.480	0.959	0.942
Typha	0.682	0.303	0.792	0.819
Rush	0.816	0.456	0.861	0.293
Halfa	0.728	0.317	0.840	0.683
Pennisetum	0.882	0.704	0.966	0.166
Agave	0.795	0.613	0.985	-3.855
Only Alginate at pH=8	0.5751	0.3121	0.762	-0.9972
Only Alginate at pH=2.5	0.6924	0.3029	0.762	-3.2828

The only model having a coefficient of determination (R^2) close to the 1.000 was the Korsmeyer-Peppas model (Table 4). Then, it was applied to the release extent of less than 60% (Korsmeyer *et al*. 1983; Arora *et al*. 2011; Malana and Rubab 2013). The curves obtained by this model, in an acidic medium, demonstrated that they were composed of two linear portions with different slopes, and each portion exhibited a coefficient (R^2) that was acceptable. Therefore, at least two phenomena for Diclofenac release were predicted from this model. In a first step, the AI contained in the alginate layer was released, and secondly, the AI present in the fibrous network was released. These two steps were

influenced by the parameters: fibrous network, level of fines, specific volume, concentration of alginate in the protective layer, and the solubility of Diclofenac and alginate. The calcium alginate carapace was more soluble in a basic medium than in an acidic medium, thus influencing the release percentage, which was relatively fast comparatively. For percentages lower than 60%, a straight line was fit to the model, with valid correlation coefficients (Fig.11, 12).

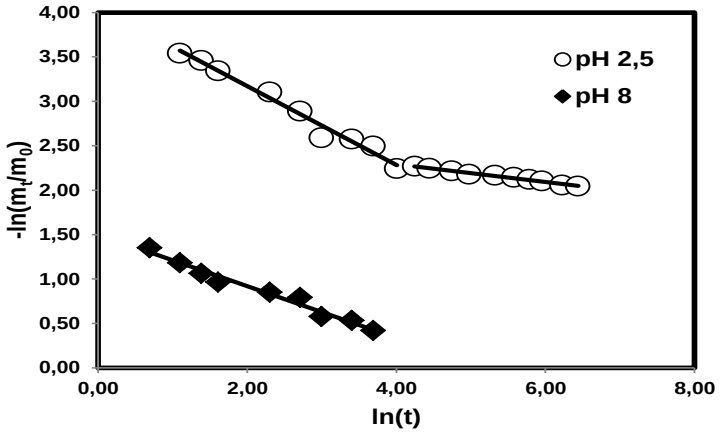


Fig. 11. Korsmeyer-Peppas model of the release of the AI encapsulated in alginate in an acidic or a basic medium

Table 5. Korsmeyer-Peppas Model Coefficients

		Korsmeyer-Peppas (R^2 and *n*)			
Matrixes	pH	R^2	*n*	R^2	*n*
Only Alginate	8	0.987	0.275		
	2.5	0.981	0.443	0.988	0.100
Kraft + e_1	8	0.934	0.414		
	6	0.944	0.444		
	2.5	0.976	1.236	0.982	0.205
Kraft + e_2	8	0.986	0.534		
	6	0.969	0.439		
	2.5	0.973	0.944	0.986	0.274
Kraft + e_3	8	0.979	1.228		
	6	0.988	0.653		
	2.5	0.935	1.455	0.987	0.373

In the case of matrixes from paper made from Moroccan fibers, there was a similarity with the representations according to the kinetic model of Korsmeyer-Peppas (Fig. 13). In a basic medium, plots have a single straight-line; however in an acidic medium, they exhibited two straight lines having two different slopes. The values of *n* (Table 5) suggest the presence of several release mechanisms.

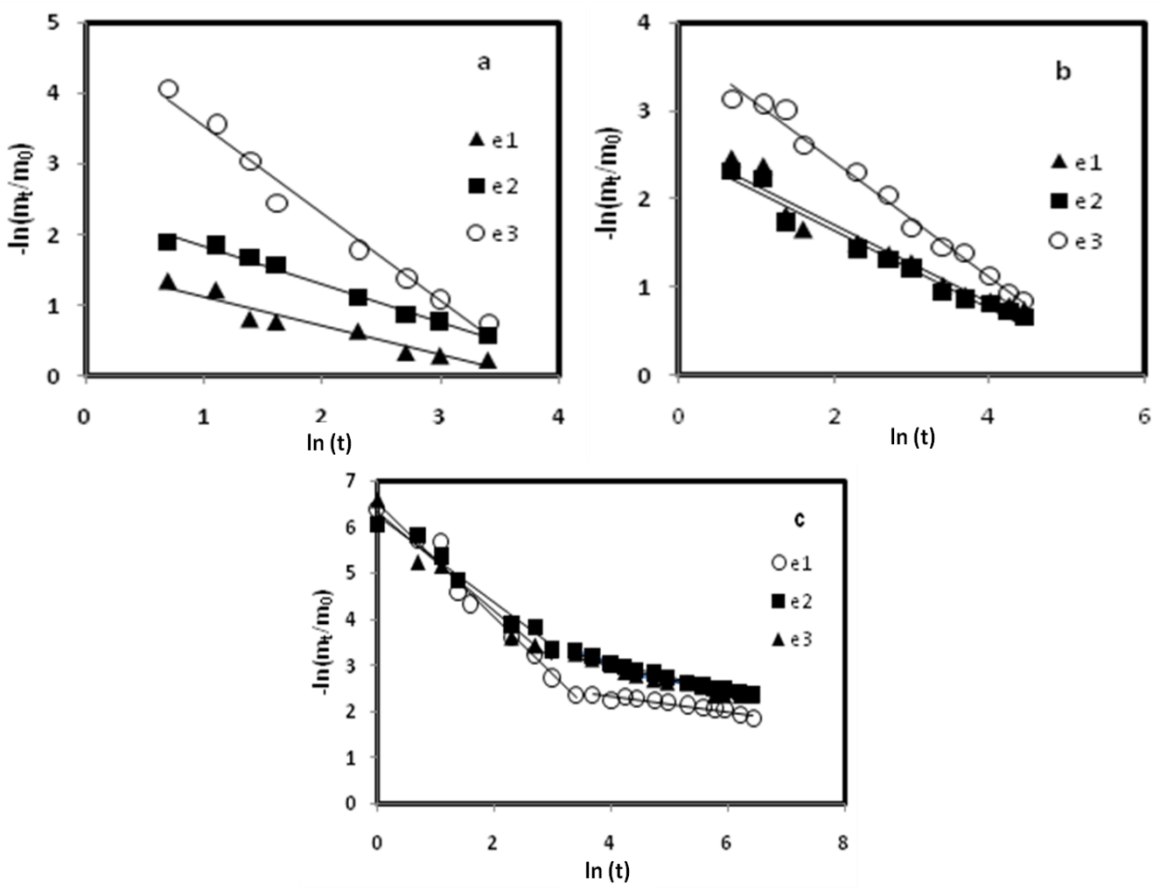


Fig. 12. Representation of Korsmeyer-Peppas model: Kraft coated alginate with different membranes (e_i) and a pH of a) 8, b) 6, and c) 2.5

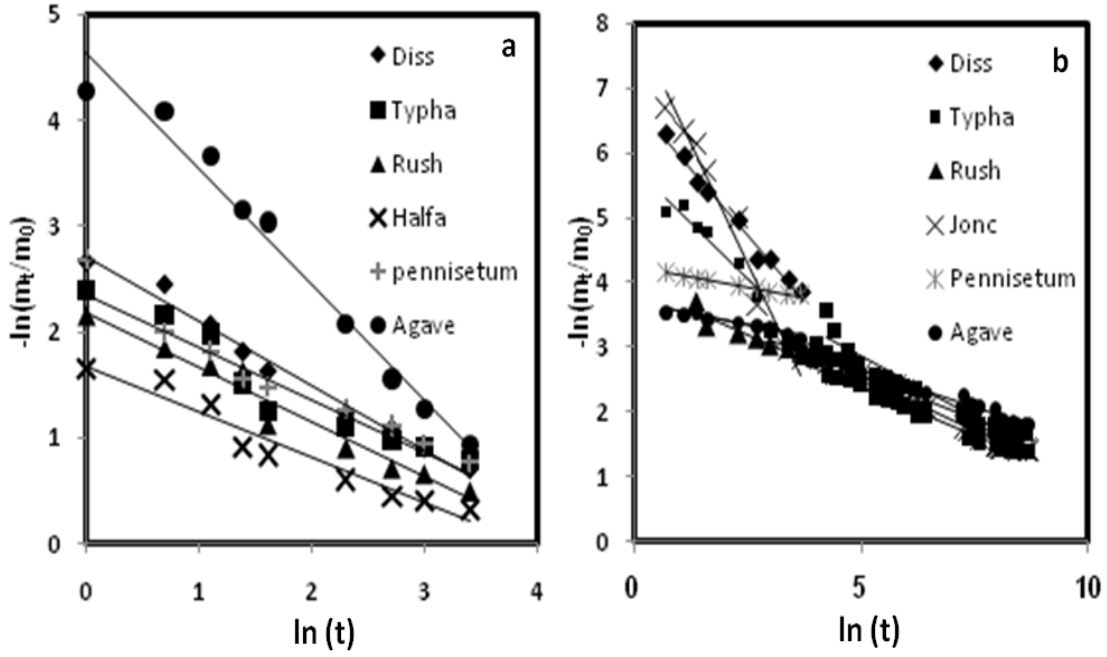


Fig. 13. Representation of the Korsmeyer-Peppas model: Paper from Moroccan plants coated alginate with the same membrane and at the pH of a) 8 and b) 2.5

Table 6. Korsmeyer-Peppas Model Coefficients for the Moroccan Plant Matrices

		1st portion of the curve (a)		2nd portion of the curve (b)	
Matrixes	pH	R^2	*n*	R^2	*n*
Diss	8	0.986	0.61		
	2.5	0.984	0.828	0.937	0.422
Typha	8	0.928	0.499		
	2.5	0.928	0.686	0.921	0.303
Rush	8	0.964	0.52		
	2.5	0.839	0.31	0.986	0.33
Halfa	8	0.945	0.429		
	2.5	0.965	1.527	0.981	0.298
Pennisetum	8	0.953	0.51		
	2.5	0.987	0.127	0.980	0.399
Agave	8	0.963	1.211		
	2.5	0.938	0.124	0.974	0.236

The different values of *n* suggest the presence of several mechanisms in the release of the AI from the matrixes. Examination of Tables 5 and 6 revealed that there were all types of release mechanisms were displayed: Fickian diffusion, diffusion-erosion, case II, and super case II. In the presence of a hydrophilic and insoluble AI, coated with a hydrophilic alkali-soluble matrix, individual delivery systems were generated. There was a clear influence of the fibrous network, the concentration of alginate, and the pH of the medium on the release mechanism.

The values of *n* obtained from the kinetic model, Korsmeyer-Peppas, were between 0.1 and 1.527. These values reflect the coexistence of several phenomena involved in the release of Diclofenac from these matrixes. The following cases can be distinguished according to the Korsmeyer-Peppas model:

- When $n < 0.5$ in the second portion of the Korsmeyer-Peppas model (Table 6, part b): This occurred in an acidic medium after the release of a first portion of the AI, on the surface and within the membrane. This second phase involved the release of the AI in the fiber core which, after hydration, migrates to the membrane and diffuses through. This case corresponds to a diffusion mechanism controlled by the membrane.
- When $n = 0.5$ in the Fickian diffusion mechanism: This mechanism happens in a basic medium except in the case of agave. The solubility of both the AI and the membrane facilitated the diffusion of the water, which caused the fibrous network to swell and solubilized the AI located within. This means that after introducing the matrix into the medium, a network of strongly hydrated/swollen fibers, surrounded by a gel of macromolecules, are formed. These well solvated polyanions have very large hydrodynamic volumes which will be excluded accordingly. This state would facilitate the diffusion of the AI into the medium.
- Values between 0.5 and 1 were found in the case of matrixes made with the lignocellulosic fibers, kraft fibers, dis grass, and *Typha*, in an acidic medium. The handsheets made from these fibers had high specific volumes and roughness (Table 1). The alginate film that was deposited (membrane) on the surface of these papers was brittle and irregular. Therefore, it would readily introduce more discontinuity and more porosity to the matrix. In addition, once in the medium, water could penetrate and swell the network. This is the explanation for the release of the AI by a combination of both diffusion and erosion mechanisms.

CONCLUSIONS

1. The present study has developed a new delivery system using only natural and renewable products: lignocellulosic fibers from woods or plants and sodium alginate from brown algae. The process is simple and easy in comparison to other methods for producing delivery systems for time-release mechanisms. The proposed delivery system requires fewer steps, and it is very economical.
2. The influences of paper composition, the sodium alginate concentration, and the pH of the release medium were investigated. The different matrixes tested exhibited different and reproducible CR profiles, where various release mechanisms were displayed.
3. The application of the Korsmeyer-Peppas kinetic model determined the release mechanisms for the AI. The specific release properties of the fiber/alginate system with the pH of the medium were determined, and it was found that this delivery system is a good candidate for a gastro-resistant vector.

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