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Crosslinking of alginic acid/chitosan matrices using polycarboxylic acids and their utilization for sodium diclofenac release

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Abstract

Three different ratios of alginic acid/chitosan matrices of ratios 3/1, 1/1 and 1/2, respectively, were crosslinked in their dry state using citric acid (CA)/sodium hypophosphite (SHP) at different conditions controlling the crosslinking process such as citric acid concentration, citric acid/sodium hypophosphite molar ratio as well as time and temperature of reaction. Results indicate that such matrices were crosslinked efficiently on curing at 180 °C for 9 min in presence of CA/SHP ratio 1 and the citric acid concentration of 0.6 based on the weight of any matrices. The crosslinked matrices were characterized by investigating their swelling properties, FT-IR and thermalgravimetric analysis. Furthermore, such crosslinked matrices were tested as drug release for sodium diclofenac.

Keywords: Alginic acid; Chitosan; Crosslinking; Citric acid; Swelling properties; Drug release; Sodium diclofenac

1. Introduction

Sodium alginate and chitosan are naturally occurring polysaccharides having much attention in drug delivery system for their non-toxicity, and excellent biocompatibility (Bajpai & Tankhiwale, 2006a; Tao, Sun, Su, Chen, & Roa, 2006). Chitosan is a polysaccharide cationic in nature, composed mainly of (1,4) linked 2-amino-2-deoxy-β-D-glucan and soluble in acidic solutions, but insoluble in alkaline solutions. Alginic acid is a linear copolymer of (1,4) linked-D-mannuronic and -l-guluronic acid residues arranged in a non-regular block wise pattern. Both the amino groups in the chitosan molecules and carboxyl groups in the alginate molecules are pH-sensitive materials as drug carriers (Bajpai & Tankhiwale, 2006a). Chitosan and sodium alginate were extensively crosslinked by many crosslinking agents such as glutaraldehyde, epichlorohydrin and divalent calcium salts to prepare polymeric hydrogels as drug carriers capable to swell considerably in aqueous medium (Chatchawalsaisin, Podczeck, & Michael Newton, 2004; Kanti, Srigowri, Madhuri, Smitha, & Sridhar, 2004; Lai, Abu'Khalil, & Craig, 2003; Ye, Wang, Liu, & Tong, 2005).

Polycarboxylic acids having three or more carboxyl groups such as citric acid are believed to crosslink carbohydrates such as cellulose (Welch & Andrews, 1994) and starch (Fahmy, Samaha, Abo-Shosha, & Ibrahim, 2004; Gaffar, 2002) by reaction with hydroxyl groups of these substrates through an anhydride intermediate mechanism.

On the other hand, alginic acid is anionic in nature and soluble in neutral and alkaline solutions, but insoluble in acidic solutions (Gotoh, Matsushima, & Kikuchi, 2004). Moreover, sodium diclofenac (Fig. 1) is anti-inflammatory drug and dissolved in aqueous solutions.

Keeping in mind the above background, the present work is undertaken with a view to crosslink different ratios of alginic acid/chitosan matrices in their dry state using citric acid/sodium hypophosphite at different factors controlling the crosslinking process such as citric acid concentration, citric acid/sodium hypophosphite molar ratio as well as the reaction time and temperature. Furthermore, the crosslinked substrates will be characterized

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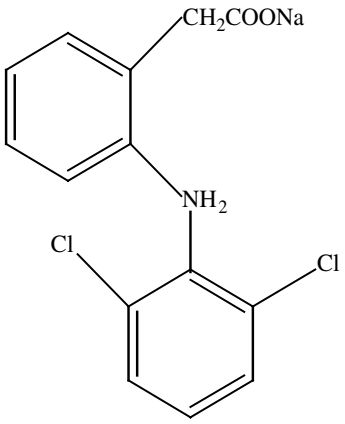

Fig. 1. Chemical structure of sodium diclofenac.

by investigating their swelling properties, FT-IR and thermalgravimetric analysis and utilized as drug carriers.

2. Experimental

2.1. Materials

Chitosan (CT) of high molecular weight and degree of deacetylation 85%, and alginic acid (AL), China. Sodium diclofenac is of pharmaceutical grade, China. Citric acid (CA), sodium hypophosphite monohydrate (SHP) and other chemicals were of reagent grade.

2.2. Preparation of crosslinked alginic acid/chitosan matrices (CALCTM's)

In a Petri-dish, a sample of 4 g of AL or its admixtures with CT was vigorously mixed with certain amounts of CA and SHP. The dish was then placed in a circulated air oven at specified temperatures, 140–190 °C, to affect crosslinking reaction. After certain times, 6–30 min., the crosslinked sample was cooled at room temperature, disintegrated, ground and stirred vigorously in 150 ml of 2% aqueous acetic acid solution for 60 min with occasional shaking to dissolve uncrosslinked chitosan, followed by thorough washing with water, drying at 50 °C for 24 h and final drying over P_2O_5 for at least 48 h before analysis.

2.3. Swelling studies

The water uptake capacity of each sample was determined by immersing the pre-weighed dry crosslinked matrices in deionized water as swelling media of pHs 1.2 (0.1 M HCl/NaCl) and 7.4 (0.1 M phosphate buffer) at 37 °C. At regular intervals the hydrated samples were taken out from the swelling media and weighed immediately after blotting the surface water with a filter paper. Weighing was continued until a constant weight. The percentage water content of the sample was calculated as follows:

$$\% \text{ Water content} = (\text{Final weight} - \text{initial weight})/\text{initial weight} \times 100$$

2.4. Drug loading

Sodium diclofenac was loaded in CALCSM's as follows. 0.5 g of any of these CALCTM's was added to a 100 ml stoppered glass bottle containing 50 ml of a 0.3% of sodium diclofenac (w/v) aqueous solution at pH's of 1.2 or 7.4. The bottle was shaken at 150 rpm for 75 min. Then the content of the bottle was filtered on a sintered glass crucible (G3), and the concentration of sodium diclofenac in the filtrate was determined colorimetically at the maximum wave length of absorption of that drug which was 276 nm using a photoelectric colorimeter "photoelectric colorimeter" (Model 581-china). The amount of sodium diclofenac entrapped in the matrices was calculated from the difference between the total amount of sodium diclofenac added and the sodium diclofenac found in the filtrate.

2.5. In vitro release studies

To study the release profiles of the sodium diclofenac loaded into the dried CALCTM's, the drug releasing assays were performed for 4 h at 37 °C. The pH of the releasing medium within the first 2 h was adjusting at pH 1.2, to mimic the gastric district, then the pH was raised up to 7.4, to mimic intestinal fluid and maintained at this value for 2 h (Bajpai & Tankhiwale, 2006b). All the sodium diclofenac release studies were carried out in triplicate every a time interval of 15 min, where 3 ml of solution was withdrawn and spectrophotometrically assayed.

2.6. Analysis and test methods

The % yield was calculated as follows:

$$\% \text{ Yield} = I/E \times 100$$

where: I, weight of AL and CT before the crosslinking reaction; E, weight of the dry purified crosslinked matrix.

The carboxyl content of crosslinked matrices was assessed using acid–base titration according to a reported method (Yang & Wang, 2000). The nitrogen content was determined by the Kjeldahl method. Infra Red (IR) Spectroscopy was carried out using BRUKER IR Spectrometer. Thermalgravimetric analysis (TGA) was carried out at a temperature range starting from 50 to 1000 °C under nitrogen atmosphere with heating rate of 10 °C/min using Perkin-Elmer TGA-7.

3. Results and discussion

It is believed that CA crosslinks cotton and starch via reaction with the hydroxyl function groups of these substrates through an anhydride intermediate mechanism in the presence of sodium hypophosphite monohydrate as a catalyst (Fahmy et al., 2004; Welch & Andrews, 1994). With a view towards the preparation crosslinked matrices for drug

release, different weight ratios of AL/CT have been crosslinked in their dry state using CA/SHP. Factors affecting crosslinking process were studied. Results obtained along with appropriate discussion follow.

3.1. Factors affecting crosslinking AL–CT matrices

3.1.1. CA to ALCTM weight ratio

Fig. 2 shows the effect of CA to ALCTM weight ratios on both the carboxyl contents and percent yield of those CALCTM's. For a given set of conditions, it is clear that increasing the ratio to 0.6 is accompanied with increasing both the carboxyl content and percent yield. Higher ratios (0.8–1.2) have a little effect on increasing the carboxyl contents, however the yields decreased probably due to the formation of water soluble hydrolyzed CALCTM's (Fahmy et al., 2004; Gaffar, 2002; Wing, 1996).

Carboxyl content of AL, 439 meq/100 g; AL/CT, 1; CA/SHP, 1; % *N*, 3.6; curing temperature, 180 °C; curing time, 9 min.

3.1.2. SHP/CA molar ratio

Fig. 3 shows the effect of SHP/CA molar ratios on the carboxyl contents as well as the percent yield of the CALCTM's. It is clear that, the absence of SHP from the crosslinking medium results in a high carboxyl content and a low percent yield of CALCTM's whereas introducing it leads to a contrast effect. This can be associated with the role of SHP in catalyzing ester crosslinking reactions and buffering the crosslinking system (Andrews, 1990; Welch, 1990), thereby decreasing the acidity of the system and minimizing the soluble hydrolyzed CALCTM's. This situation remains true up to a SHP/CA molar ratio of 1, beyond which the extent of crosslinking decreases. This can be associated with the increase in alkalinity of the system, giving rise to breaking of some ester links (Rowland, Brannan, & Gallagher, 1967), thereby decreasing the ester crosslinking.

Carboxyl content of AL, 439 meq/100 g; AL/CT, 1; % *N*, 3.6; CA to ALCTM weight ratio, 0.6; curing temperature, 180 °C; curing time, 9 min.

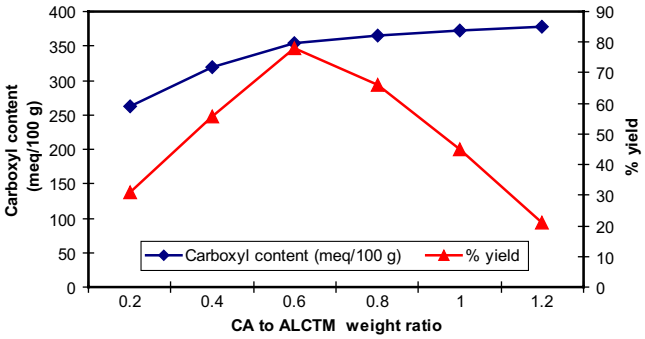

Fig. 2. Effect of CA to ALCTM weight ratios on both the carboxyl contents and percent yields of CALCTM's.

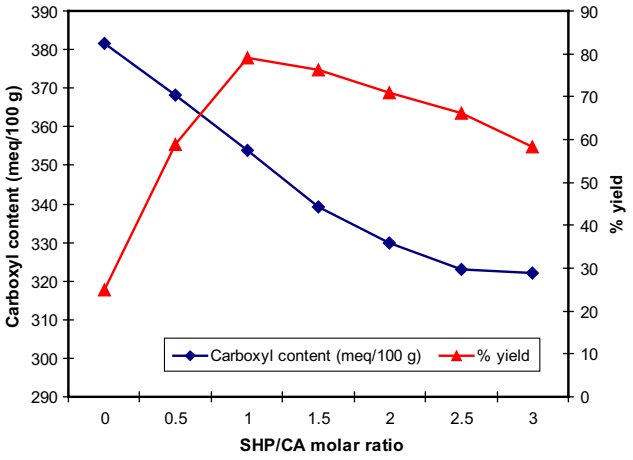

Fig. 3. Effect of SHP/CA molar ratio on both the carboxyl contents and percent yields of CALCTM's.

3.1.3. Curing temperature

Fig. 4 shows the effect of curing temperature on both the carboxyl content and the percent yield of the CALCTM's. It is clear that raising the thermofixation temperature from 160 up to 180 °C for 9 min brings about a significant increasing in both the carboxyl contents and the percent yields which is a direct consequence of the enhancement in the extent of CALCTM,s esterification with CA. Beyond 180 °C and up to 200 °C, a decrease in carboxyl content and percent yield occurs accompanied with a little charring of the product due to thermal degradation and dehydration of CALCTM's (Gaffar, 2002).

Carboxyl content of AL, 439 meq/100 g; AL/CT, 1; % *N*, 3.6; CA to ALCTM weight ratio, 0.6; SHP/CA molar ratio, 1; curing time, 9 min.

3.1.4. Curing time

Fig. 5 shows the effect of curing time on both the carboxyl content and the percent yield of the CALCTM's. It is obvious that increasing the curing time, under the

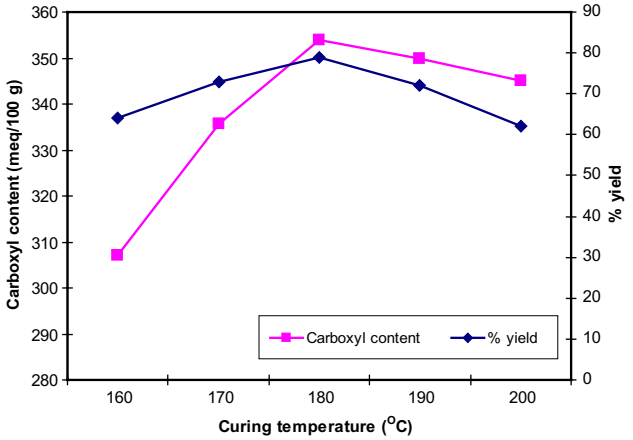

Fig. 4. Effect of curing temperature on both the carboxyl contents and percent yield of CALCTM's.

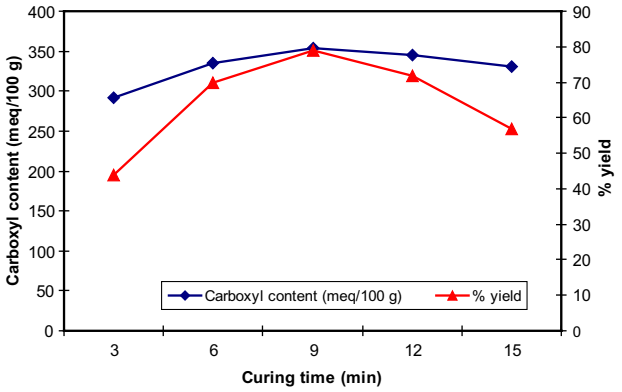

Fig. 5. Effect of curing time on both the carboxyl contents and percent yield of CALCTM's.

conditions employed, up to 9 min results in a noticeable increase in both the carboxyl content and the percent yield reflecting the enhancement in estrification of CALCTM's. Beyond 9 min and within the range studied, the percent yield as well as carboxyl contents decrease accompanied with formation of little coal which can be attributed to the increase in the extent of the thermal degradation and dehydration of CALCTM's (Gaffar, 2002).

Carboxyl content of AL, 439 meq/100 g; AL/CT, 1; % *N*, 3.6; CA to ALCTM weight ratio, 0.6; SHP/CA molar ratio, 1; curing temperature, 180 °C.

3.1.5. AL/CT weight ratios

Conditions employed in crosslinking of AL/CT of weight ratio 1 with CA/SHP were extended to include other ratios. Fig. 5 shows the effect of the variation in AL/CT weight ratios on both the carboxyl contents and the percent yields of CALCTM's. It is obvious that increasing AL/CT weight ratio leads to an increasing in the carboxyl content of that crosslinked matrices accompanied with a decreasing in the percent yield reflecting the carboxyl content of AL itself and its ability to be thermally degraded than CT under these employed conditions.

3.2. Characterization of CALCTM's

The aforementioned prepared crosslinked matrices designated in (see Table 1) as M1, M2 and M3 were subjected to characterization by investigating their swellabilities, FT-IR spectra and thermalgravimetric analysis of M2, as a representative of the prepared CALCTM's.

Table 1
Effect of AL/CT weight ratios on both the carboxyl contents and percent yield of CALCTM's

AL to CT weight ratio	Designation	Carboxyl content (meq/100 g)	% *N*	% Yield
3/1	M1	469	2.85	71
1/1	M2	354	3.6	79
1/2	M3	201	4.1	85

Carboxyl content of AL, 439 meq/100 g; AL/CT, 1; CA to ALCTM weight ratio, 0.6; SHP/CA molar ratio, 1; curing temperature, 180 °C; curing time, 9 min.

3.2.1. Swellability

Matrices M1, M2 and M3, were subjected to swell in HCl/NaCl buffer of pH 1.2 followed by transferring into sodium phosphate buffer of pH 7.4. The percent water uptake of these matrices at such pH's were plotted in Fig. 6. It is clear that: (a) increasing the pH of the medium from 1.2 to 7.4 is accompanied by increasing the swellabilities of all matrices regardless the AL/CT ratio and (b) regardless the pH, increasing the AL/CT ratio enhances such swellabilities.

This can be explained in terms of the nature of bonds inside the matrices structure. The most important forces are: (a) hydrogen bonding, (b) ionic bonds between the amino groups and carboxyl groups and (c) ester crosslink bonds between AL and CT as well as inside each of AL or CT, as a result of reaction with CA/SHP (Fahmy et al., 2004; Welch & Andrews, 1994). It seems that ionic bonding is the most governing forces in swelling. That is, at pH 1.2, crosslinked matrices exhibit minimum swelling as the amino groups of CT is protonated, to form $-NH_3^+$ groups and the electrostatic interaction of carboxyl groups, –COOH, of AL with that protonated amino groups of CT is strengthened and the matrices will have compact structures accompanied with minimum water uptake. In contrast, the slightly alkaline pH 7.4 results in a deprotonated $-NH_2$groups of chitosan whereas the carboxylic groups of alginates will be ionized to produce negatively charged carboxyl groups, $-COO^-$ groups and consequently, weaker electrostatic interactions between the two polymers chains will be formed leading to more opened matrices structures and more swellabilities (Bajpai & Tankhiwale, 2006c; Gonza'lez-Rodrý'guez, Holgado, Sa'nchez-Lafuente, Rabasco, & Fini, 2002). Indeed, increasing the AL/CT ratio will increase the matrices swellability at pH 1.2 but with low extent compared with that at pH 7.4.

3.2.2. FT-IR spectra

Fig. 7 shows FT-IR spectra of the crosslinked matrix M2. It is obvious that the most characteristic bands are

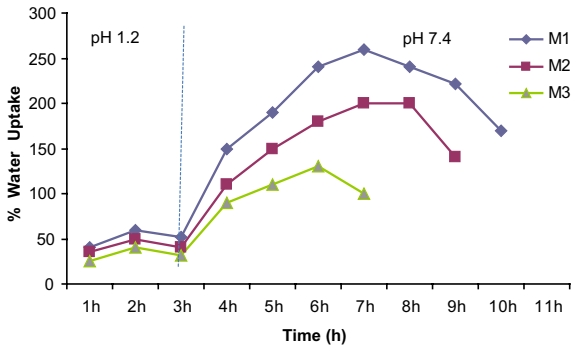

Fig. 6. Percent water uptake of M1, M2 and M3 as a function of time at pH 1.2 and 7.4.

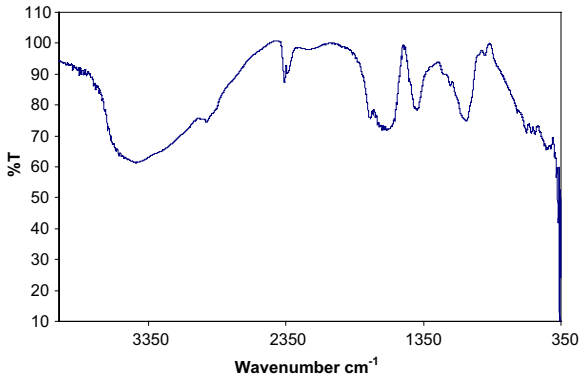

Fig. 7. FT-IR of M2.

3447 cm^{-1} confirming the presence of –OH and –NH stretching vibration in state of overlapping and 2927 cm^{-1} corresponding to C–H stretching of methyl or methylene group of chitosan and sodium alginate, 1597 cm^{-1} corresponding to N–H bending of primary amine, asymmetric stretch at 1407 cm^{-1} belongs to a carboxylate salt of sodium alginate and 1738 cm^{-1} corresponding to an ester carbonyl band of citric acid.

3.2.3. Thermalgravimetric analysis

Fig. 8 shows three curves representing the TGA of chitosan, alginic acid and CALCTM. It is obvious that the TGA of each curve consists of three parts; the first one is a dehydration stage which starts from 50 °C and ended at 158.76, 145.17 and 142.9 °C with a loss of weight 16.2%, 10.806% and 9.487% for chitosan, alginic acid and CALCTM, respectively. The second part is a thermal degradation stage resulting from pyrolysis which starts from 158.76, 145.17 and 142.9 °C and ended at 244.4, 337.76 and 439.73 °C with loss of weight of 40.095%, 60.593% and 60.162% for chitosan, alginic acid and CALCTM, respectively. The third part represents the conversion of the remaining materials to carbon residues which ends at 586.53, 535.06 and 624.64 °C with weight loss of 41.064%, 25.532% and 26.477% for chitosan, alginic acid and CALCTM, respectively. From the above discussion, it can be concluded that the residual weights at the end of the combustion process are 2.648%, 3.069% and 3.874% at final degradation temperatures of 586.53, 535.06 and 624.64 °C for chitosan, alginic acid and CALCTM, respectively, reflecting the thermal stability of CALCTM compared to chitosan and alginic acid.

3.3. Utilization of CALCTM' s for sodium diclofenac release

The effect of Al content and pH on the release of sodium diclofenac by M1, M2 and M3 matrices is shown in Fig. 9. It is obvious, under the conditions studied and for a given set of conditions, that: (a) the sodium diclofenac release is much higher at pH 7.4 than 1.2. and (b) the % release follows the descending order: M1 > M2 > M3. The higher the

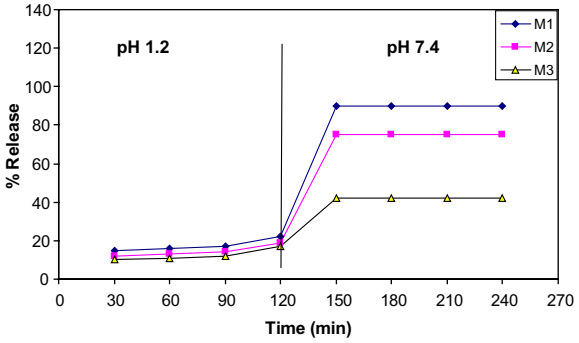

Fig. 9. Effect of Al/CT ratio and pH on the release of sodium diclofenac.

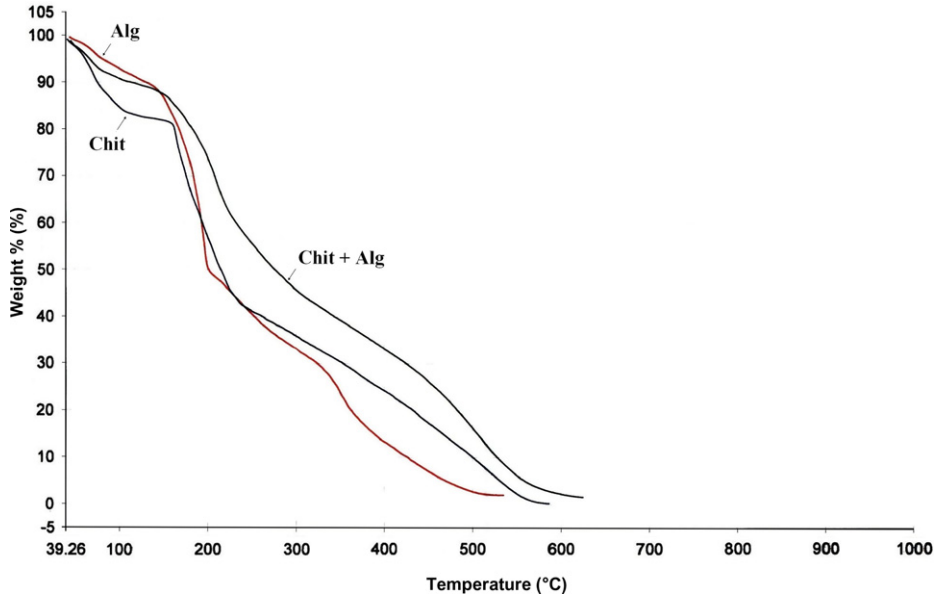

Fig. 8. TGA of Al, CT and M2.

swellability the higher the release of sodium diclofenac will be. Logically, the diffusion of the drug is easier in more opened – swelled structure than that in more compact structure (Bajpai & Tankhiwale, 2006c; Gonza'lez-Rodrý'-guez et al., 2002).

4. Conclusions

- Matrices of AL/CT (having AL/CT weight ratios of 3/1, 1/1 and 1/2) were effectively crosslinked in the dry state CA/SHP at 180 °C for 9 min using equal weight ratio of CA/SHP at an acid/matrix weight ratio of 0.6.
- Increasing the AL/CT ratio of the crosslinked matrices increases the matrices swellabilities. The latter is lower at pH 1.2 than that at pH 7.4.
- The crosslinked matrices can be used as carriers for sodium diclofenac and the higher the alginic acid content, the higher the release percent will be.
- Releasing of sodium diclofenac by the aforementioned crosslinked matrices is much higher at pH 7.4 than at 1.2.

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