K-CARRAGEENAN / SODIUM ALGINATE INTERPENETRATING NETWORK BEADS FOR THE INCORPORATION OF KETOPROFEN AS A POTENTIAL DRUG DELIVERY SYSTEM

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Polysaccharide-based interpenetrating network beads obtain by ionotropic gelation of k-carrageenan and sodium alginate were designed for the encapsulation of Ketoprofen, to ensure an improved drug release. Different mass ratio of the two polymers were used to obtain the particles by cross-linking the polymers solutions with CaCl2 and KCl. Chemical characterization of beads was assessed through FT-IR spectrometry and UV-VIS spectrometry was employed to determine encapsulation efficiency and drug release profile. Swelling studies showed a higher degree in simulated intestinal fluids than in simulated gastric fluid. Results have displayed that bi-component beads are a versatile drug delivery system.

Keywords: interpenetrating polymer network, k-carrageenan, sodium alginate, ketoprofen

1. Introduction

Active pharmaceutical delivery systems are materials used in the process of distribution of chemical compounds or drugs, enzymes, or proteins to obtain a therapeutic effect. By selecting the proper drug delivery system, we can improve drug action in the body, increase the efficiency of the treatment and reduce side effects of the drug. It can also protect the drug from the hydrolysis or other changes in the gastrointestinal tract. Different approaches have been pursued to find more efficient assembling for different kinds of drugs, within the last decades, using polymers [1–4].

Manifolds natural polymers have been engaged for the development of particles for controlled drug delivery systems due to their profitable characteristics such as low cost, renewability, biodegradability, and non-toxicity [5], [6]. Also, biopolymers represent a sustainable advantage compared to synthetic polymers because there are renewable resources [7], [8]. Some examples of natural

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hydrophilic polymers are psyllium [9], agar [10], gelatin [11] and alginate [12]. In part, because of their properties such us biocompatibility and biodegradability, natural hydrophilic polymers are widely applied in pharmaceuticals and food industry and medicine [7], [13].

One of the usual polymers used in pharmaceutical studies is alginate as an excipient in newly developed release carrier forms like tablets, suspensions, capsules and beads because of its therapeutically advantages, such as lower side effect and mucoadhesive properties [14], [15].

Polymeric-based gels are formed by interpenetrating networks of their molecular chains obtaining a three-dimensional system with similar compatibility to human tissue. The mechanical properties are enhanced by crosslinking of these systems [16]. The interpenetrating polymer network (IPN) is the product of mixing two or more polymers solutions in which one of them is synthesized and/or cross-linked resulting a physically entangled three dimension network in order to manufacture gel beads that are suitable candidate for controlled drug release due to prolonging the release of the product in the body [17–19].

Sodium alginate (SA) is both a biopolymer and a polyelectrolyte that is naturally obtain from brown alga [20], [21]. It can be described as a linear hydrophilic copolymer composed of α-L-guluronic (G) and (1→4)-linked β-D-mannuronic (M) acid monomers [5], [10], [15], [20].

Due to it mucoadhesive property, gels beads with sodium alginate, as the main material, have been applied to increase the contact time between the drugs and mucosal layer [5], [14], [22], [23]. The capacity of the natural polymer sodium alginate to form hydrogels easily, in moderate conditions, is attributed on one hand to the ionotropic gelation due to the interaction of the crosslinkers like bi- and trivalent ions such as Ca^{2+} and Al^{3+} with G blocks residues and on the other hand, to the polyelectrolyte complexation with a different charged biopolymers [6], [24]. Thus, an encapsulation method through the assembling of particles of sodium alginate solution which contain the dissolve drug by dropping into the $CaCl_2$ cross-linking solution was developed but this method favors the obtaining of large beads with uneven contour [14]. This approach is suitable for encapsulation of hydrophobic drugs like ketoprofen and, in his research, Sohail [14] sprayed both alginate with drug solution and also the $CaCl_2$ solution obtaining the microspheres by aerosols technique. Also, del Gaudio [25] encapsulated ketoprofen and ketoprofen lysinate in alginate beads obtained by prilling, with $CaCl_2$ as crosslinking agent, in order to study drug control release.

A large variety of compounds including drugs (gastro-irritant, non-steroidal, anti-inflammatory drugs) [7], [14], [26], hormones (insulin) [27], proteins, bacteria, enzymes and cells have been entrapped in alginate hydrogel [14], [23], [28], [29].

Carrageenan (CG) is another important anionic, hydrophilic polysaccharide extracted from marine algae Rhodophyceae which is made of alternately linked D-galactose and 3,6-anhydro-D-galactose units [17], [24], [30]. Carrageenans are divided, based on the number and position of sulfate groups, in kappa (k), iota (i), and lambda (λ) [31], [32]. They have the ability to develop a three-dimensional network of double helix of polymeric chains, after cooling even at room temperature, by crosslinking with the proper cations (K^+, Ca^{+2}) [33] and, when suitable conditions are fulfilled, it easily jellifies by crosslinking with the help of ions (Li^+, $K^{+,}$ Na^+, Cs^+ and Ca^{+2}) obtaining strong gels by coil to helix transition with improved swelling capacity [33], [34] that can be used in controlled released technology [31], [35]. Carrageenan is used as food additive for its thickening, emulsifying properties, and as stabilizing agent and also in the pharmaceuticals industry as an excipient and formulations component for controlled drug release due to its gelling ability [30], [35]. Moreover, k-CG, because of it biodegradability, insures cell adhesion and proliferation [33].

Hydrogel systems manufactured from these two natural polymers were employed to encapsulate hormones (insulin) [5], drugs [16], [34], proteins [36] and as a cell delivery system [37]. Rasool et al [38] incorporated lidocaine in a drug delivery carrier made with k-CG, SA and different molecular weights of polyethylene glycol and (3-Aminopropyl)triethoxysilane as a cross-linker. 5-Fluorouracil loaded SA microbeads were coated with chitosan followed by another coating with k-CG layer and showed a slower drug release than SA and SA with chitosan particles and also avoided the burst of the drug [39].

Ketoprofen (Ket) is an anionic, non-steroidal anti-inflammatory drug with low aqueous solubility (95μg/mL). It is employed in the treatment of inflammation, to relieved the pain in rheumatism (rheumatoid arthritis) and as local analgesic [14], [15], [40] and could manifest serious side effects mainly in the gastrointestinal region but after encapsulation this inconvenience is reduce [15].

The encapsulation and release profile of Ket and α-tocopherol from poly(styrene-co-maleic acid) copolymer nanoparticles was studied by Deak and al [41] and the release of Ket in alkaline medium was 70% while in gastric condition was 30%. The co-former, cysteine and Ket were used to formulate pharmaceutical salt to enhance the solubility of the active ingredient [42]. Ket was encapsulated in various delivery system such as IPN beads obtained from polyacrylamide-g-locust bean gum with SA [18], another interpenetrated system obtained from SA and polyacrylamide grafted k-carrageenan was employed for delivering ketoprofen to the intestine [17] and a copolymer beads like acrylate-based copolymer [43]. In his research, Yamada et al [44] incorporated calcium salt of Ket in core microparticles with Eudragit L100 and coated these microparticles with ethylcellulose and carboxymethylethylcellulose to obtain a suitable drug release.

The purpose of this research was to develop and evaluate the carrageenan/alginate IPN gel beads as a promising controlled drug release system for Ket, with the goal of improving solubility and stability of the drug in gastro intestinal simulated conditions. The IPN gel beads will protect Ket in the gastric intestinal tract due to the presence of SA which has a strong acidic resistance [45].

We studied the influence of the SA type by using low- and medium-molecular weight sodium alginate as well as the effect of the different weight ratios between k-CG and SA on the drug release profile. In our study, we used k-CG due to its property to form strong gels under mild condition to protect drug from acidic conditions of stomach. The encapsulation efficiency of Ket from the bi-composite polymers network was also assessed.

2. Materials and methods

2.1. Materials

Medium-molecular-weight sodium alginate (Alginic acid sodium salt from brown algae), low-molecular-weight sodium alginate, k-Carrageenan (predominantly κ and lesser amounts of λ carragennan), Ketoprofen (≥98%), potassium chloride (KCl), sodium chloride (NaCl), hydrochloric acid ≥37% (HCl) and potassium phosphate monobasic (KH_2PO_4) were purchased from Sigma-Aldrich. Calcium chloride anhydrous powder ($CaCl_2$) was purchased from Merck, Germany and sodium hydroxide pellets (NaOH) from Riedel-de Haën.

2.2. Method

IPN hydrogel bead preparation

The ketoprofen loaded SA/k-CG IPN gel beads were prepared via the ionotropic gelation technique [46], (fig. 1) and it is a modified method from a previously reported study of Kolesnyk et al [47] to obtain a protein delivery system by emulsification method and $CaCl_2$ as a crosslinking agent. Yu et al [16] and Li et al [34] both used SA/k-CG beads, in different mass ratio for the adsorption of ciprofloxacin and used also the crosslinking agent, $CaCl_2$. The crosslinking time was 8 hours and 12 hours. Bovine Serum Albumin was encapsulated in Sarıyer et al [36] research in SA/k-CG IPN gel beads, using different mass ratio of $CaCl_2$ and KCl and different pH of synthesis. In this conditions, the encapsulation efficiency increased, and the release of the protein was controlled with no burst.

To the best of our knowledge, Ket was not incorporated in this kind of IPN beads so far.

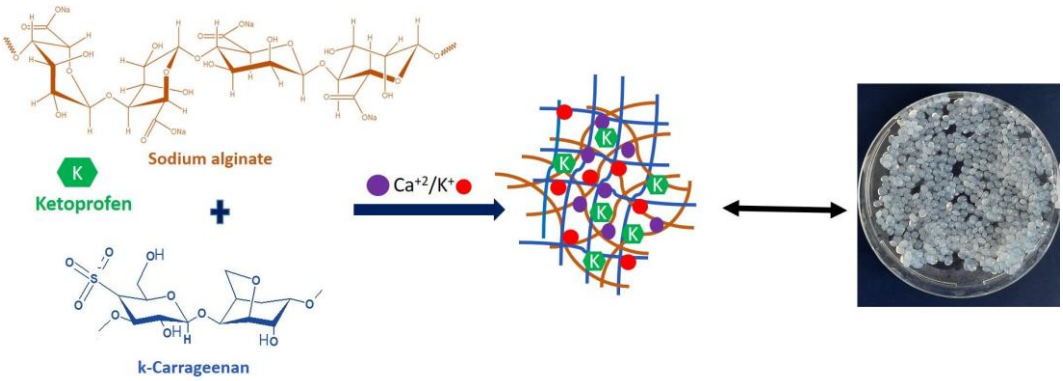

Fig. 1. Schematic illustration of the IPN beads synthesis

The ionic crosslinking process take place between two polymers chains, once the polymeric solution is push out into ionic solution of Ca^{+2} and K^{+} that have a synergistic action. These ions exchange Na^{+} from the polymer [17].

SA is usually cross-linked with Ca^{+2} through the G-blocks to form the 'egg-box' structures by ionic inter-chain bonding and carrageenan interacts with K^{+} creating electrostatic attraction with the sulfate esters but the jellify process is due to the intermolecular glue-like effect of the K^{+} ions [24], [35]. However, k-CG and Ca^{+2} can create a link due to electrostatic attraction [16]. For this reasons we used a mixed solution of $CaCl_2$ and KCl so that the two polysaccharides can form their networks in order to obtain the IPN gel beads. Nevertheless, we have to take into consideration the existence of the hydrogen bonding between these two biopolymers due to high amount of carboxylate groups of SA and hydroxyl groups of CG, creating a crosslinking network by hydrogen bonding. This network sustains the stability of the structure and decreases the intermolecular space between two chains of the two natural polymers [16].

The first step was to separately prepare, the polymeric solutions of k-CG and SA of 2% concentration. The k-CG solution was prepared by magnetic stirring and heated in a water bath at temperature range 75-80 °C until the polymer was dissolved and SA solution was prepared at room temperature, overnight. For the preparation of the other bi-component polymeric solutions certain amounts of k-CG and SA were added in 100 mL distillated water to obtain the following SA and k-CG weight ratios: SA/k-CG = 3:1; 1:1; 1:3 and for a better handling of SA/k-CG IPN beads preparation we used the next weight ratios: 3:0.2; 3:0.4; 3:0.8. The polysaccharide solutions were mixed and the bath temperature was maintained at 60-75 °C.

The second step was to dissolve 5 mg of Ket into 20 mL polymeric solution. All the solutions were magnetically stirring and heated at 40-60 °C

except for the SA solution with Ket, that occur over night at room temperature, by stirring.

To obtain the Ket-loaded k-CG/SA-IPN hydrogel beads, 20 mL of the previous drug-polymer solutions was extruded drop wise through syringe into 70 mL of mixed 0.3 M $CaCl_2$ and 0.45 M KCl ($CaCl_2$:KCl=1:1 volumetric ration). The hydrogel beads were let for 30 min into the reaction solution for hardening. The preparation of blank hydrogel beads followed the same protocol without the Ket incorporation. The IPN gel beads were filtered, wash with distillated water and then air dried at room temperature.

3. Characterization of the hydrogel beads

3.1. Fourier transform infrared (FT-IR) spectroscopy

FTIR analysis was performed in a FTIR-ATR Bruker VERTEX 70 spectrometer. The samples were scanned between 4000-600 cm^{-1} wavenumbers range with 32 scans for each spectrum at room temperature.

3.2. Encapsulation efficiency (EE) of the ketoprofen

EE of ketoprofen was determined by evaluating the amount of the drug encapsulated in the IPN hydrogel beads by UV-VIS-NIR spectrophotometer UV 3600 Shimadzu provided with a quartz cell having a light path of 10 mm. The UV spectra were measured at λ = 260 nm. The Ket assay was obtain using a calibration curve with concentrations of Ket between 0.001 and 0.025 mg/mL.

The EE was calculated using the following formula 1 [47]:

$$EE\ (\%) = \frac{\text{Loaded amount of the ketoprofen}}{\text{Total ketoprofen amount}} * 100 \quad (1)$$

3.3. Swelling studies

The swelling behavior of the IPN hydrogel beads was conducted in different media, simulated intestinal fluid SGF at pH=6.8 and simulated gastric fluid SIF at pH=1.2 using a shaking water bath GFL 1083. A certain amount of air-dried hydrogel beads was placed in media solution at 37 °C for 24 hours, under shaking. The swelled beads were removed at predetermined time interval and weighed after drying the surface using filter paper [5].

The swelling degree (SW) of the hydrogel beads was calculated using formula 2 [5] :

$$SW\ (\%) = \frac{\text{weight of wet beads} - \text{weight of dried beads}}{\text{weight of dried beads}} * 100 \quad (2)$$

3.4. Drug release study

The drug release behavior of the IPN hydrogel beads were studied into a fully automated dissolution bath USP Apparatus 1 (708-DS Agilent) connected to

an auto controlled multi-channel peristaltic pump (810 Agilent) and at a UV-VIS spectrophotometer (Cary 60) with 1 mm flow cell and UV-Dissolution software. The drug release studies were conducted in a dialysis membrane bag in which was introduced a certain amount of air-dried IPN hydrogel beads and 5 mL of buffer solution of SGF, pH 1.2 and SIF, pH=6.8 respectively. The dialysis membranes were immersed in 200 mL buffer solution at 37 °C and the spindles rotation speed was 75 rpm.

At different time intervals the dissolution media were automatically extracted, and the amount of drug released was determined using UV-Vis spectrophotometer at 260 nm.

4. Results and discussions

4.1. Structural information of the obtained hydrogels

All batches of drug-loaded beads and plain hydrogel beads along with pure drug were analyzed by FT-IR spectroscopy to obtain information about the composition of the IPN gel beads. The FT-IR spectra of the Ket-loaded beads were compared with those of Ket, SA, k-CG and SA/k-CG beads.

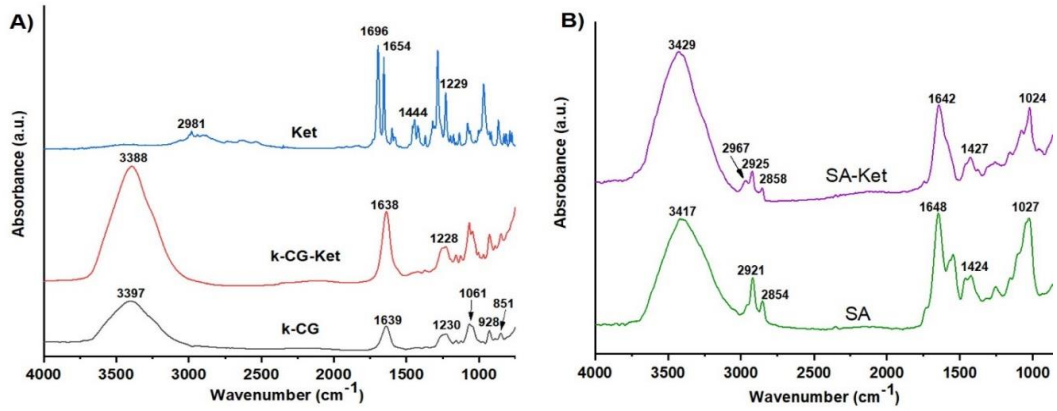

Fig. 2. FT-IR spectra of A) Ket powder, k-CG beads and drug loaded K-CG beads and B) SA beads and Ket loaded SA beads.

The FT-IR spectrum for Ket (fig. 2A) shows the characteristic peak at 1696 cm^{-1} which belongs to the C=O stretching vibration of the carboxylic acid while the peak at 1654 cm^{-1} is due to stretching vibration of the –C=O from ketonic groups [48], [49] and the stretching vibration of –C-H at 2981 cm^{-1} [49]. Also, the band at 1229 cm^{-1} is the stretching vibration of C-O; C–O–H in-plane bend and the peak at 1444 cm^{-1} is attributed to the asymmetric deformation of CH_3 [42].

The spectrum of plain k-CG (fig. 2A) bead showed the following characteristic peaks at 1230 cm^{-1} and 851 cm^{-1} for ester sulfate stretching vibration and for D-galactose-4-sulfate, and the peak at 928 cm^{-1} is attributed for 3,6-anhydro-D-galactose while the peak at 1061 cm^{-1} is due to glycosidic linkage. The broad band at 3397 cm^{-1} represents the stretching vibration of the –OH groups [5], [10], [17]. The peak observed at 1639 cm^{-1} is attributed to the carboxylic group (O=C-OH) stretching [34].

The FT-IR spectrum of unloaded SA beads, (fig. 2B), shows the broad peak at 3417 cm^{-1} that is correlated to the stretching vibration of the –OH groups due to the intermolecular or intramolecular hydrogen bonds. The characteristic peaks at 1648 cm^{-1} and 1424 cm^{-1} can be assign to the stretching vibration of C-O from –COO group (asymmetric and symmetric stretch) [5], [34], [39] and the peaks observed at 2921 cm^{-1} and 2854 cm^{-1} are due to the symmetric and asymmetric –C-H aliphatic stretching vibrations [38], [39], [50].

FT-IR spectra of blank SA/k-CG beads (fig. 3 and fig. 4) present the characteristic peaks of –OH, carbonyl functional groups, glycosidic linkage and ester sulfate groups that exist in the structure of both biopolymers with no significant difference only with slight shifting of the peaks and a modification of the peak intensity caused by the mixing of the polymers and the production of cross-linking [16], [34] without electrostatic or covalent interactions [5].

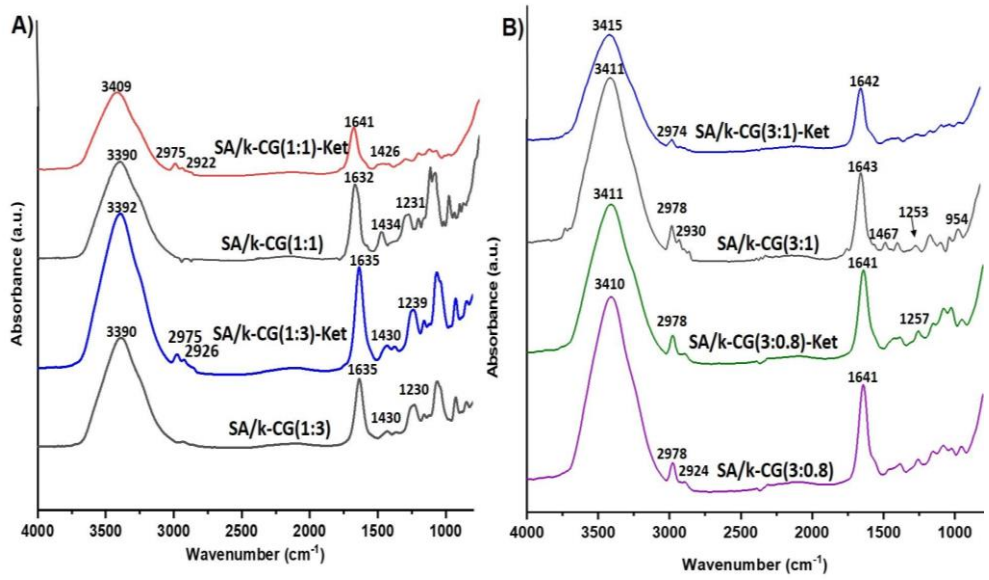

Fig. 3. FT-IR spectra of A) loaded and blank SA/k-CG (1:1) and SA/k-CG (1:3) beads and B) loaded and blank SA/k-CG (3:1) and SA/k-CG (3:0.8) beads

When the k-CG content degreases, the peak from 2921 cm^{-1} from SA beads is shifted to 2974, 2978 and 2977 cm^{-1} in SA/k-CG=3:1, 3:0.8, 3:0.4 and 3:0.2. Also, the intensity of the characteristic peaks from kCG are reduce and band at 1424 cm^{-1} from SA beads is at ~1434 cm^{-1} in SA/k-CG=1:1 and SA/k-CG=1:3 and at 1470 cm^{-1} in SA/k-CG=3:1. Spectra of drug loaded SA/k-CG=1:1 and SA/k-CG=1:3 particles presents two pairs of peaks at 2975 cm^{-1} with 2922 cm^{-1} and at 2975 cm^{-1} with 2926 cm^{-1}, respectively. Additionally, a new peak appears at 2967 cm^{-1} in SA-Ket beads (fig. 2 B) from Ket. For the other drug loaded particles there are no important changes, only shifting of peaks.

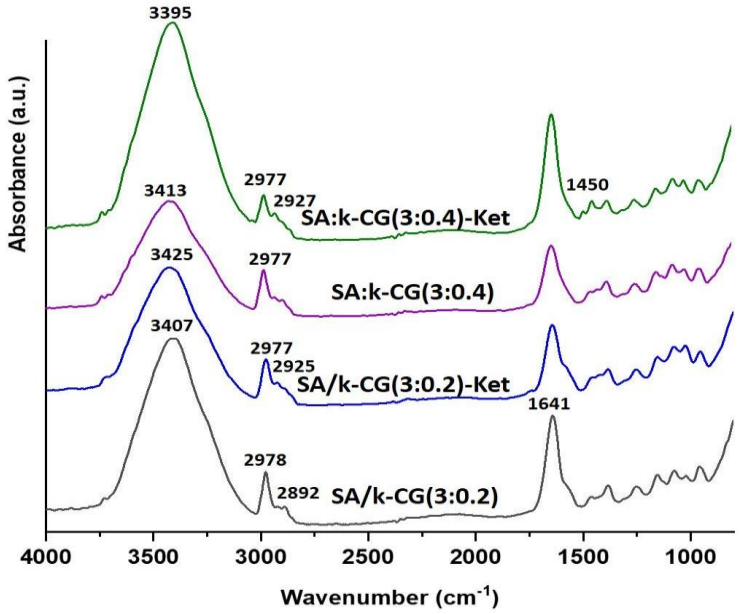

Fig. 4. FT-IR spectra of Ket loaded and unloaded SA/k-CG (3:0.4) and SA/k-CG (3:0.2) beads

4.2. Encapsulation efficiency (EE) of ketoprofen

The EE of Ket was estimated from the cross-linking solution after the drug-loaded IPN beads were removed. The table 1 shows the EE of the Ket in SA and k-CG hydrogel beads and in SA/k-CG IPN hydrogel beads. The k-CG beads had a better entrapment of the drug than SA beads. For the IPN beads, the encapsulation of Ket depends on the ratio between the two polymers, the highest values being recorded for the SA/k-CG (3:0.2) system. When the content of SA is increased in the IPN beads, the EE of the drug increases. This behavior can be explained by different hydrogel stability. Also the molecular weight of SA influences the drug entrapment.

Table 1.

Encapsulation efficiency (EE) of ketoprofen in different IPN beads

System	Encapsulation efficiency (%)	System	Encapsulation efficiency (%)
k-CG	45		
SA	34	SA-low	25
SA/k-CG(1:3)	37	SA low/k-CG(1:3)	30
SA/k-CG(1:1)	36	SA low/k-CG(1:1)	24
SA/k-CG(3:1)	46	SA low/k-CG(3:1)	31
SA/k-CG(3:0.8)	33	SA low/k-CG(3:0.8)	43
SA/k-CG(3:0.4)	43	SA low/k-CG(3:0.4)	36
SA/k-CG(3:0.2)	51	SA low/k-CG(3:0.2)	43

4.3. Swelling studies

The swelling behavior was performed on the loaded and unloaded particles with better encapsulation efficiency. All the bi-component beads showed different swelling behaviors in both simulated media (SGF, pH=1.2 and SIF, pH 6.8).

In acidic conditions, all hydrogel beads showed a low swelling rate. Moreover, for the IPN hydrogel beads this conduct is a consequence of hydrogen bonds formation between carboxylic and hydroxyl groups of the polymer which limits their swelling by decreasing the space between the polymeric chains [16] compared to their conduct in pH=6.8 (fig. 5 and fig. 6). For SA beads, this behavior is assign to the protonation of $–COO^-$ groups while in case of k-CG particles is due to the sulfate groups, which in SGF at pH=1.2, remain the same [5], [46]. All the IPN gel beads have similar swelling behavior except for the plain SA/k-CG (3:1) beads which from the beginning it has a highest swelling degree 76% in the first 15 minutes as it shows in fig. 5.

The blank k-CG beads have the lowest swelling degree (SW) during two and a half hours, 28% compared to the other beads but the SW increases up to 114% at five hours and at 145% at the end of the tested period. The same trend was for Ket loaded k-CG beads, SW at 15 minute was 3%, the lowest from all the tested beads, but with higher values after five hours, 127% and 306% at 24 hours. For all the others IPN beads, the degree of swelling during 5 hours did not vary significantly and this behavior was maintained at 24 hours. The drug loaded particles presented an increase of SW when compared with unloaded beads except for drug loaded SA/k-CG (3:1) particles that presents a decrease of SW. But from the tested drug loaded bi-component beads, SA/k-CG (3:0.2)-Ket particles exhibit the lowest SW, at 15 minutes 47% and after 2 hours was 52%.

Therefore, the swelling behavior of these beads indicated that they are suitable for protecting ketoprofen from the acidic action of the stomach.

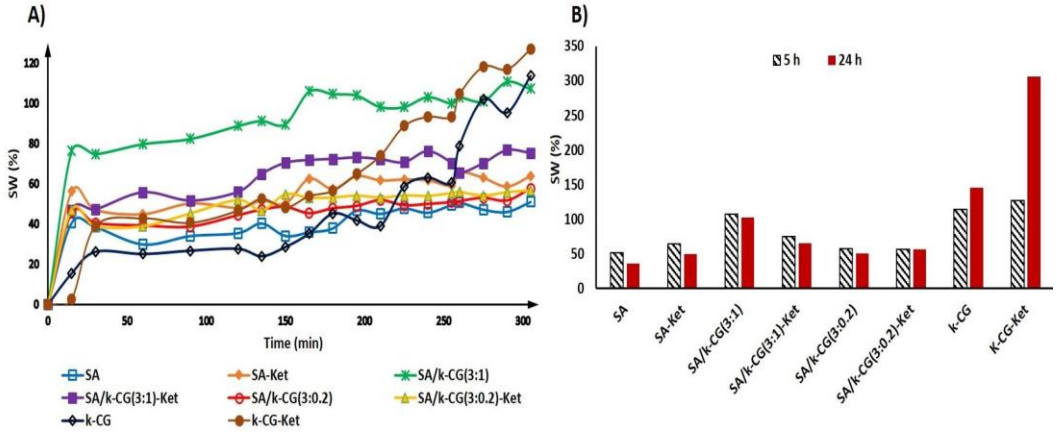

Fig. 5. Swelling behavior of the beads in SGF, pH=1.2 were A) is a detail of the swelling degree during 300 minutes and B) is the swelling behavior at 5 and 24 hours.

When changing the conditions and the IPN beads are incubated in SIF, the same bi-component beads have higher SW values as in pH=1.2; loaded and unloaded SA/k-CG=3:1 particles followed by SA/k-CG=3:0.2 loaded and blank particles. The IPN gels are swollen and can be disintegrated and this happens because of the exchange of the cross-linking calcium ions bounded to the polymeric chain of alginate with non-gelling ions like phosphate or Na^+ from the SIF [51]. In addition, in the bi-component beads, this behavior is due to the intense repulsive forces between the sulfate groups on the k-carrageenan and carboxylate groups on the alginate which decreases the electrostatic interaction [5], [35].

As showed, in fig. 6, in SIF condition, plain k-CG and Ket-loaded k-CG beads present the highest swelling degree within 60 minutes (80% and 96%) this happens because k-CG is an ionic polymer which have a pH-independent sulfate groups and particles made of these polymers are dissociated throughout the pH scale [46]. Additionally, it was notice that the value of swelling degree of IPN beads increased as the k-CG component increases, similar behavior as showed in Mahdavinia's research [46]. SA/k-CG (3:1)-Ket composite hydrogel exhibited a greater SW on the entire tested period. Also, all drug loaded beads have SW values above the plain polymers particles, the exception is SA-Ket particles which has a SW higher values after 2 hours and at the end of the trail period, the highest values are for SA and SA-Ket. The SW of the evaluated beads in SIF environment was higher than in SGF.

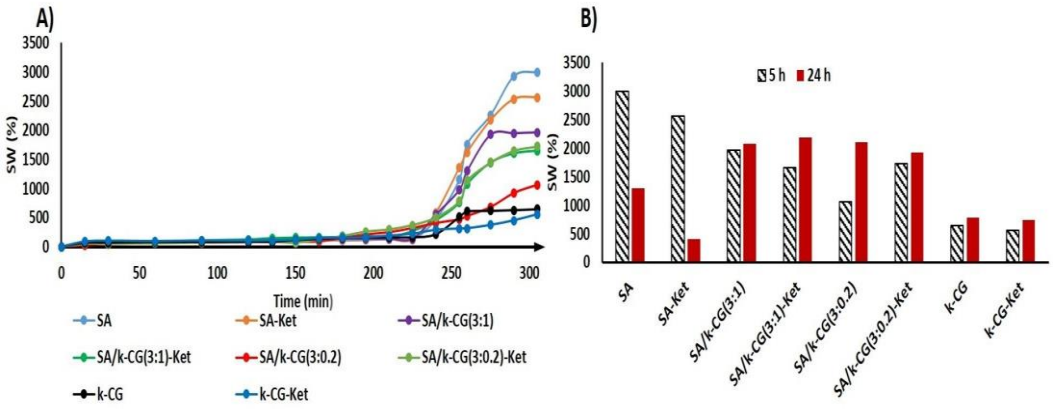

Fig. 6. Swelling behavior of the IPN beads in SIF at pH=6.8 were A): swelling behavior for 300 minutes and B): swelling behavior at 5 and 24 hours

4.4. Drug release study

The release of Ket from the beads was studied by adding a certain amount of dried beads in different dissolution medium (SGF and SIF).

Due to the fact that alginate and k-carrageenan are hydrophilic polysaccharides, it is anticipated that beads obtain from these polymers would easily disintegrate in aqueous medium causing a fast release of the amorphous drugs [7]. Alginate gels are pH-sensitive and in an acidic environment it becomes insoluble and shrinks due to the protonation of the carboxyl groups in the polymeric chains [52] as mentioned at swelling tests, which keeps Ket trapped within the hydrogel matrix.

In fig. 7 it can be observed that the maximum release of the drug in SGF, pH=1.2, is from the SA/k-CG (1:1) IPN hydrogel, in 15 minutes it is 22% and in the first 2 hours it exhibits a 46% release, followed by a 54% release at the end of the test. At pH=1.2 the SA is protonated into the insoluble form of alginic acid [16], [52], the hydrogen bounding with k-CG increases and, as the swelling behavior under this conditions showed, the beads are shrinking and the release of the drug is slowed down. Moreover, SA becomes a gel and blend with k-CG as studied illustrated and due to the ionization of the $-SO_4^{2-}$ groups from k-CG, hydrogels that includes k-CG, depicted low reactivity in salt solutions [16].

Also, a burst release of Ket from all polymers matrices is noticed. Drug release from IPN formulation in the first 15 minutes was the same (16%) for SA/k-CG (1:3) and SA/k-CG (3:1) with the lowest burst from SA/k-CG (3:0.2), 12%. After 2 hours it was found to be around 30% for both polymer matrices SA/k-CG (1:3) and SA/k-CG (3:1) and only 21% from SA/k-CG (3:0.2). At the end of the 24 hours period, the drug release is 34% from SA/k-CG (1:3) and 32%

from SA/k-CG (3:1) beads and only 23% drug release from SA/k-CG (3:0.2) bi-component beads.

The percentage of Ket released from SA particles was found to be 24% in the first 15 minutes and 46% after 2 hours and 50% after 8 hours but this value remains approximately the same until the end of the 24 hours. From k-CG beads, the drug release was 17% after 15 minutes and 36% after 2 hours and by the end of the 24 hours trial, it was 41%, the same value since the end of 8 hours period. Drug solubility in pH=1.2 (0.1N HCl medium) is 0.13 mg/mL [53] that might explain the curve from the fig. 7. It is insoluble in acidic medium but being encapsulated in this type of beads helps it solubility. This indicates that most of the Ket in the developed beads would be available to be absorbed within the intestinal tract and protected from the gastric fluid especially in the first hour. Therefore, this IPN hydrogel beads are suitable for protecting Ket in the stomach conditions.

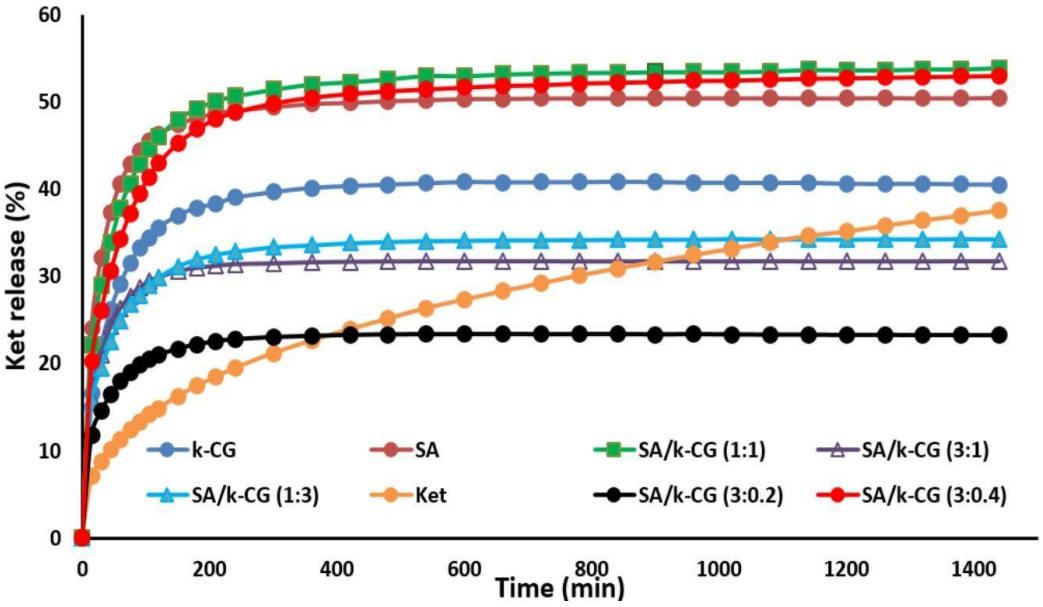

Fig. 7. Ket release profile in SGF at pH=1.2 for 24 hours

In SIF conditions (fig. 8), the release of Ket is promoted by the repulsion force between the negative groups of the two natural polymers from the IPN bead and also from the ion-exchange between Na^+ and phosphate from the dissolution medium and the Ca^{2+} and K^+ from the polymers matrices [5], [16], [34]. As it has been seen in the swelling tests, all the tested IPN gel beads present a greater swelling capacity than to the incubation in acidic environment, however, the release of Ket wasn't dictated by the swelling process.

Fig. 8 illustrates that the percentage of drug release within 3 hours is almost the same for all the beads, with slightly differences. After this period of time, the release increases and the highest value of the drug being discharged from SA beads. The release of Ket was slower from hydrogel matrices in comparison with pure Ket that was completely dissolved in SIF. The increasing of the amount of k-CG, increases the drug release from the system (fig. 8) probably because of the growth of the electrostatic repulsive of the two polymers from the IPN hydrogel particles. Drug release rate in simulated intestinal fluid has no significant variation than the behavior in the simulated gastric media. The lowest drug release in the first 15 minutes, is for SA/k-CG=3:0.2, 11% and the highest, 21%, for SA/k-CG=1:3. At the end of the 24 hours trial period, the lowest Ket release is from SA/k-CG=3:0.2 (24%) and the highest drug release, (53%) is from SA/k-CG=1:3 beads, taking into account only the bi-component beads.

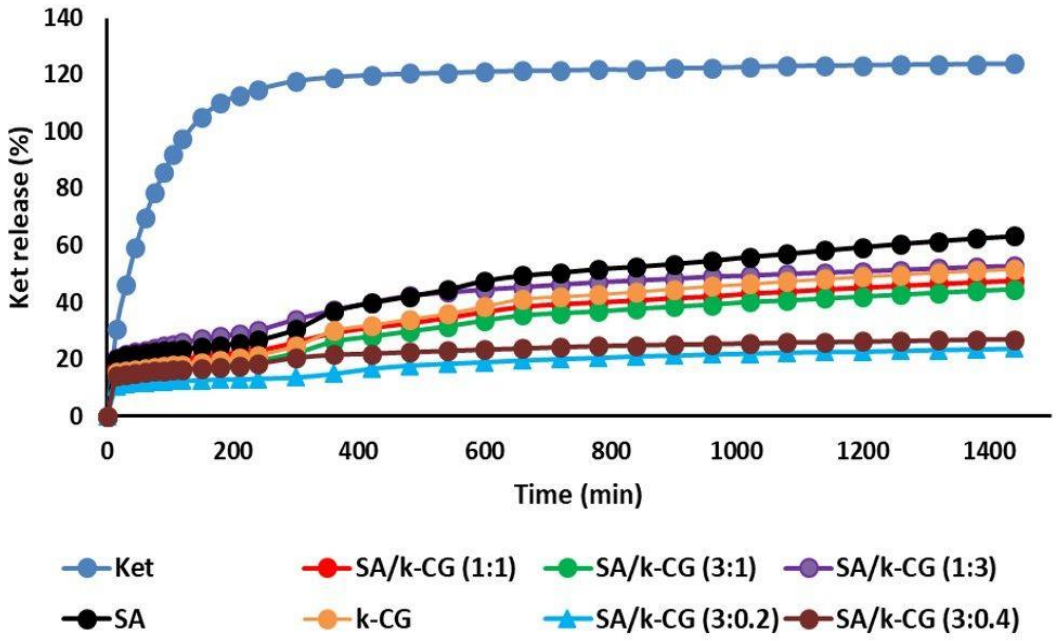

Fig. 8. Ket release profile in SIF at pH=6.8 for 24 hours.

5. Conclusions

In this study, polysaccharide-based interpenetrating network gel beads cross-linked with calcium chloride and potassium chloride as drug delivery carrier for Ket were produced. The highest percentage of encapsulation for Ket was 51% in case of SA/k-CG (3:0.2) beads and the lowest was in SAlow/k-CG (1:1) beads

(24%). The IPN SA/k-CG beads were able to entrap Ket and protect the drug in acidic environment (SGF). At higher pH, in SIF, all the SA/k-CG beads provided a gradually release with slightly differences from all the studied IPN beads for up to 2 hours, the lowest is from SA/k-CG (3:0.2) and at the end of the 24 hours period, the highest drug release, from the IPN beads, is from SA/k-CG (1:3), about 53%. In conclusion, the IPN SA/k-CG beads are possible drug delivery carriers with improved performance of natural polymers beads gels for ketoprofen.

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