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Synthesis of pH-responsive hydrogel based on PVP grafted with crotonic acid for controlled drug delivery

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In the present study polyvinylpyrrolidone (PVP) was grafted with crotonic acid (CrA) in order to obtain novel hydrogels which are pH – responsive. The grafting was performed by mixing the polymer solution with various concentrations of CrA and applying gamma radiation at different doses. The effects of the preparation conditions such as the irradiation dose and CrA concentration on the gelation process and swelling of the synthesized copolymer were investigated. The hydrogel system was used as carrier for a model drug, ketoprofen, the release behaviour of the drug from the hydrogel was monitored in two different release media (pH 1 and pH 7.2), and released amounts of ketoprofen were followed up spectrophotometrically. The release was low in the acidic medium compared to a better and extended release in the neutral medium suggesting the possibility of using this hydrogel as potential drug carrier to allow targeted release in the intestinal medium.

Key words: polyvinylpyrrolidone (PVP); crotonic acid; radiation grafting; drug delivery

1. Introduction

Hydrogels are polymeric networks that have the ability to swell considerably in aqueous media. The hydrophilic groups attached to the polymer backbone provide the hydrogel with its water absorbing characteristics. Meanwhile the crosslinking between the polymeric chains prevent it from dissolving in aqueous environment (Hennink et. Al, 2002; Hoffman, 2002; Tanaka, 1978; Shibayama and Tanaka, 1998).

These hydrogel systems have been employed in various applications including medicinal and pharmaceutical fields due to their properties of water absorbance, mucoadhesive and bio-compatibility (Rosiak et al., 1983; Peppas and Mikos, 1986; Peppas, 2004; Lugão et al., 1998, 1999; Ajji et al., 2005, 2008; Wu et al., 2011; Mozalewska, 2017; Szafulera et al., 2018). Hydrogels responding to external stimuli such as heat, pH, chemical environments and ionic strength are often referred to as "intelligent hydrogels" (Qiu, 2001). pH-responsive hydrogels have been investigated in controlled drug delivery where the release of the drug is triggered by a change in the pH of the surrounding media which could occur naturally at different sites in the human body. For example, each part of the gastrointestinal (GI) tract has its own pH value. A pH change could also be a sign of abnormality such as the tumour acidic microenvironment (Mooney, 2016). Thus, by using hydrogel pH-responsive system a targeted delivery of the drug to a specific site can potentially be achieved. For instance, the gastric pH (<3) is much lower the pH that of the intestine, so the swelling of an anionic hydrogel in the acidic stomach is minimal leaving the drug entrapped and shielded in the

polymer structure. When the system passes to the intestine milieu, the negatively charged pendant groups will repel each other causing hydrogel swelling and drug release (Du et al. 2015; Rizwan, 2017). This GI targeted delivery is useful for drugs with poor gastric stability and to reduce the irritating effect of the drug on the gastric mucosa. The hydrogels could be usually prepared from hydrophilic polymers which will be grafted with multi-functional linkers through physical, chemical or ionising irradiation methods. The irradiation techniques have the advantages of providing clean cross-linked polymers without initiator residue (Ahmed et al., 2015). The preparation of these functionalized hydrogels attracted the attention of many researchers in the world for their potential application in adrorption and separation heavy metals (Saraydin et al., 1995; Güven et al., 1999; Ajji, 2005; Ajji et al, 2005; Ajji, 2007; Ajji et al., 2009a, 2009b; Nacef et al., 2012; Saraydın et al., 2016).

Polymerization and copolymerization of crotonic acid (CrA) has been studied in the temperature range of 77-350 K. It had been found that crotonic acid monomer had not been added to radical propagating centres of a polymer chain at temperatures below 165 K. This low activity of the monomer was attributed to the shielding of the double bond by the CH group preventing the addition of acid to the radical. Nevertheless, crotonic acid can be added to propagating radicals of the chain of other monomers (acrylates) in copolymerization at temperature higher than 165 K. However the formed radical active centre of crotonic acid has the low activity because of steric hindrances created by CH3 and COOH groups (Kuzina et. al., 1992). Caykara et. al. reported on the preparation of Poly(N-vinyl-2-pyrrolidone–crotonic acid) copolymers by means of gamma-ray starting from various monomer compositions. Some properties had been presented as: surface free-energy, gelation and swelling (Caykara et al., 2004a, 2004b).

In the current investigation the hydrogels were prepared by grafting PVP with various CrA concentrations using different gamma irradiation doses. The objectives of this study are to develop a novel PVP-based hydrogel by gamma irradiation and to test its ability as a pH-responsive drug carrier. Ketoprofen was used as a model of a hydrophobic anti-inflammatory nonsteroidal drug that causes stomach irritation therefore it is preferable to be incorporated into a carrier resistant to gastric media to be subsequently released in the intestinal milieu.


2. Experimental

2.1. Materials

PVP (MW = 72000) was obtained from Merck, crotonic acid (purity > 99%) from Fluka.

2.2. Methods

Graft copolymerization

The direct radiation-induced grafting of CrA onto polyvinylpyrrolidon (PVP) was used as a preparation technique. 6 g PVA (MW = 72000) was dissolved in 90 ml distilled water and heated. Different amounts of CrA (0.2 – 4 g) were dissolved in the PVP solutions, and poured into glass tubes. The tubes containing all reactants were irradiated in air at ambient temperature using a Co^{60} Gamma cell (dose rate 3.5 kGy/h) to different doses up to 85 kGy.
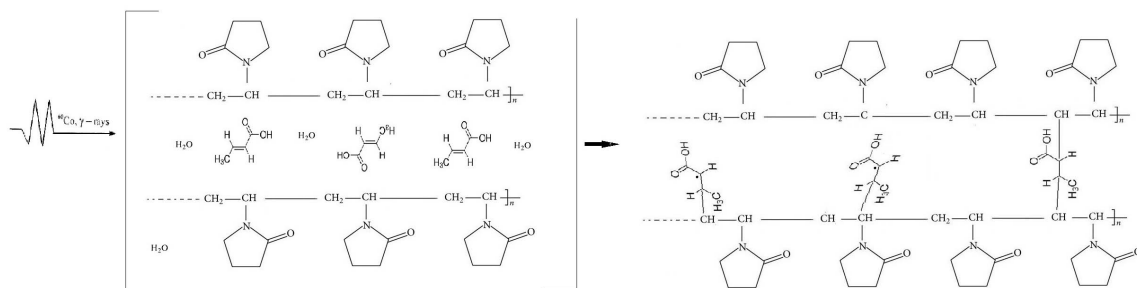
Scheme 1

Scheme 1 suggests few reaction possibilities of CrA with the polymeric chains; it might build a bridge between the polymer chains or bonded from one side with the polymeric chain and forming a free radical which could react with surrounding species.

Determination of Gelation

After drying the irradiated samples (W_o), the samples were soaked in distilled water up to a constant weight (W_S) to remove soluble and unreacted species. The hydrogels were then dried again (W_E), and the degree of gelation (%) was calculated as follows:

$$\text{Degree of gelation (\%)} = \frac{W_E}{W_o} \times 100$$

Determination of maximum swelling

After soaking of the dried hydrogel in distilled water for 3 days at least, the maximum swelling was calculated:

$$\text{Maximum swelling (\%)} = \frac{W_S - W_o}{W_o} \times 100$$

Where W_S is the weight of gel at equilibrium, and W_o is the weight of dried gel.

Loading and release of Ketoprofen

100 mg of Ketoprofen was dissolved in 10 ml phosphate buffer of around pH 7.2. The dry hydrogels were (32.2 mg, 0.2% crotonic acid) was soaked in the drug solution at room temperature until equilibrium. The PVP-g-CrA hydrogel loaded with Ketoprofen was allowed to swell in hydrochloride acid solution (pH = 1) and a 0.2 M phosphate buffer solution (pH = 7.2) to perform the release studies. The drug-loaded hydrogel was put in 25ml of 0.2 M HCl (pH = 1) for 3.5 h, then transferred into 100 ml 0.2 M phosphate buffer (pH 7.2) for 47 h. The concentration of drug was measured using an UV–VIS spectrometer, Shimadzu (type UV-1601).

3. RESULTS AND DISCUSSION

3.1. Characterization of PVP/CrA hydrogels

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Figure 1 represents the percent of gelation with respect to the irradiation dose for various concentrations of the crotonic acid. It can be seen that the gelation% increases with increasing the irradiation dose which can be explained with the increase in the crosslink density due to increasing the irradiation dose. The increase in the CrA leads to lower gelation% and raising the gelation dose. The acid might act as reaction inhibitor as this was reported in the literature as well using other types of acids (Ajji, 2005). It can also be observed that no insoluble samples were obtained for high CrA concentration at low doses compared with the samples using lower acid concentration.

FTIR spectra were recorded using a Nicolet 6700 spectrometer for the PVP raw powder, crotonic acid, and the PVP-g-crotinic acid (Figure 2). The FTIR spectra of PVP shows the following characteristic bands associated with its structure. The absorption band at 3448 cm^{-1} could be attributed to the O-H stretching vibrations. The band at 2924 cm^{-1} is due to C-H stretching vibrations, while the absorption band at 1655 cm^{-1} could be attributed to the stretching carbonyl group C=O. The peak at 1383 cm^{-1} is due to C-H bending and the peak at 1287 cm^{-1} could be due to C-N stretching vibrations. The grafted hydrogel with carboxylic acid onto the crosslinked PVP shows a threshold small peak around 1577 cm^{-1} which could be the most clear evidence of the grafting of the carboxylic acid onto PVP; this peak could be due to carbonyl group of carboxylic acid which is grafted onto PVP.

Figure 3 represents the maximum swelling with regards to the irradiation dose for various concentrations of crotonic acid. It can be seen that the maximum swelling decreases with increasing the irradiation dose which can be explained with the increase in the crosslink density due to increasing the irradiation dose that hinders the polymeric chains to expand/ move freely. The increase in the CrA concentration led to lower gelation% and higher maximum swelling. To be mentioned that at higher CrA concentration and lower doses, the samples stayed liquid or dissolved in water during the washing procedure.

The swelling behaviour of hydrogels plays an important role in controlled drug release behaviour. Therefore, it was important to investigate the effect of the pH on the hydrogel swelling. Swelling of the hydrogels in different pHs values had been performed (pHs 1 to 8).

Figure 4 represents the swelling of the PVP-g-CrA hydrogels with respect to pH values. A significant increase in the swelling can clearly be observed with increasing pH value of the solution, which indicates that drug release could be possible. This is consistent with polyelectrolyte systems, that the maximum swelling were achieved between pH 6 and 7 due to complete dissociation of acidic groups of CrA at this pH value. The disassociation constant of CrA is pK$_a$ = 4.69 (Butler, 1964). The swelling values of these hydrogels show atmost sudden increase at the pH values around corresponding pKa value.

The hydrogel swells with time achieving a plateau after almost 40 h as shown in Figure 5; it indicates the influence of the irradiation dose and CrA concentration on the maximum swelling of the prepared hydrogels as mentioned above.

Diffusion

When a hydrogel is brought in contact with water/ solutions, water diffuses into the hydrogel and the network expands resulting in swelling of the hydrogel. Analysis of the mechanisms of water diffusion into swellable polymeric systems has received remarkable attention in recent years, because of various important applications of swellable polymers in biomedical, pharmaceutical, environmental, and agricultural engineering (Karadag et al., 2005).

The following equation is used to determine the nature of diffusion of water into the hydrogels.

$$F = \left(M_t \Big/ M_\infty \right) = K t^n$$

where F is the fractional uptake at time t (M_t/ M ∞), k a constant incorporating characteristic of the macromolecular network system and the penetrate, and n is the diffusion exponent, which is indicative for the transport mechanism (Peppas and Franson, 1983). The equation is valid for the first 60% of the fractional uptake. Fickian diffusion and Case II transport are defined by n values of 0.5 and 1, respectively. Anomalous transport behavior (non-Fickian diffusion) is intermediate between Fickian and Case II. That is reflected by n between 0.5 and 1 (Peppas and Franson, 1983).

For the prepared PVP-g-CA hydrogels, Ln (F) is plotted versus Ln (t), and the results are represented in Figure 8. Diffusion exponents (n) and diffusion constants (k) are calculated from the slopes and intercepts of the lines, respectively, and are listed in Table 1.

Table 1 shows diffusion exponents (n) and diffusion constants (k) in acidic and slight alkaline media; the number (n) determines the type of diffusion. (n) is over 0.5 in neutral-alkaline media for all doses. Hence, the diffusion of water into the super absorbent hydrogels have a non-Fickian character as generally described in the literatue (Peppas and Franson, 1983; Saraydin et al., 2004).

The study of diffusion phenomena of water into hydrogels is of high value in clarifying polymer behavior. The diffusion coefficients for hydrogels can be calculated by various methods; the short time approximation method is applied for the calculation of diffusion coefficients of PVP-g-CrA hydrogels (Am Ende and Peppas, 1997). This method is valid for the first 60% of initial swelling. The diffusion coefficients of the cylindrical PVP-g-CrA hydrogels using the following relation:

$$F = 4 \left(\frac{D\,t}{\pi\,h^2} \right)^{\frac{1}{2}}$$

where D is in $cm^2\ s^{-1}$, t in s and r is the radius of a cylindrical polymer sample.

For the prepared hydrogels, F was plotted versus $t^{1/2}$ and obtained results are shown in Fig. 7, and the diffusion coefficients were calculated from the slope of the lines and listed in Table 2. A slight increment in the diffusion coefficient with the increase in the irradiation dose could be observed in agreement with the another system consisting of acrylamide-co-CrA published previously (Karadag et al., 2005)

Release of Ketoprofen

The chemical structure of Ketoprofen is illustrated in following scheme:

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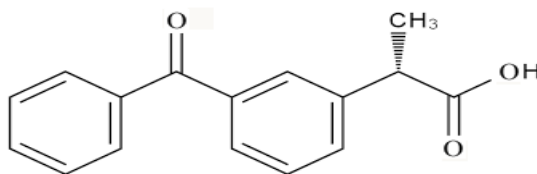
Hydrogen bonds between the carboxylic functional groups of ketoprofen and the carboxylic group of the grafted crotonic acid could be formed as well as with the amide groups of PVP; also the keto functional group might interact with partially positively charged hydrogen of the carboxylic or amid groups. Hydrophobic interactions are also possible between the alkyl backbone of the polymer and the benzene rings, which are weak attractive forces.

The release experiments were carried out in acidic solution (pH 1) which is almost similar to that of fasted- state gastric medium for 3.5 h and at buffer solution of pH 7.2 which simulates the pH of the intestinal medium for 47 h.

Figure 8 shows the drug release behaviour of PVP-g-CrA hydrogel as a function of time at pH 1 and 7.2. The figure shows that there is very limited drug release at pH 1 whereas the drug release occurs as soon as the copolymer transferred into the buffer solution of pH 7.2. The results show that the drug release is pH dependent, and could be considered as pH responsive release system. This could be explained with the presence of strong hydrogen bonds in the acidic medium due to protonated hydroxyl groups, which hinders the release of ketoprofen. In alkaline medium the hydrogel network expands due to the decrease in hydrogen bonds and consequently the drug might be released as the experiments showed.

Conclusion

Polyvinylpyrrolidone was grafted successfully with CrA obtaining novel pH – responsive hydrogels. The effects of the reaction conditions such as the irradiation dose and CrA concentration on the gelation process and swelling were investigated. The hydrogel system was also tested as carrier for a model drug, ketoprofen, and the release of the drug was monitored in two different release media (pH 1 and pH 7.2). The release was limited in acidic medium relatively to a higher and extended release in the neutral medium suggesting the possibility of using this hydrogel as potential drug carrier to allow targeted release in the intestinal medium.

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Table 1. diffusion exponents (n) and diffusion constants (k)

0.2% crot. Dose↓	pH = 1			pH = 7.2		
	n	r^2	k	n	r^2	k
45	0.54	0.99	-2.81	0.54	0.99	-2.87
65	0.49	0.99	-2.64	0.59	0.99	-3.15
85	0.45	0.99	-2.21	0.51	0.99	-2.55

Table 2. diffusion coefficients for PVP-g-CrA hydrogels

0.2% crot. Dose↓	pH = 1		pH = 7.2	
	D	r^2	D	r^2
45	0.075	0.99	0.073	0.99
65	0.066	0.99	0.073	0.99
85	0.083	0.99	0.083	0.99
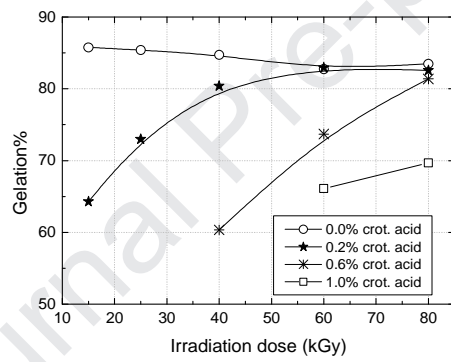
Figure 1. Gelation% vs. the irradiation dose for various concentrations of CrA
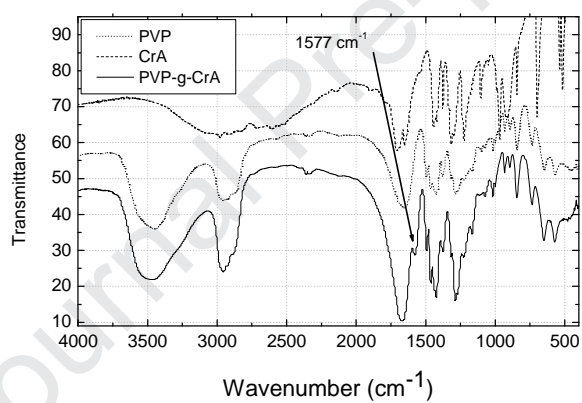
Figure 2. FTIR spectra of PVP, crotonic acid, and PVP-g-CrA
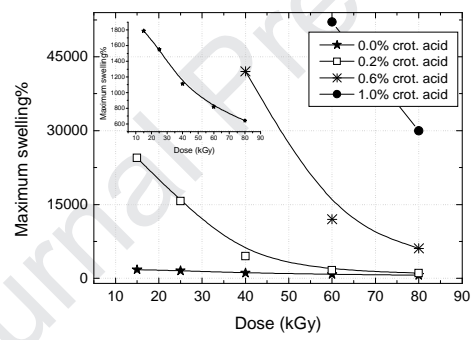
Figure 3. Swelling % vs. the irradiation dose for various CrA concentration
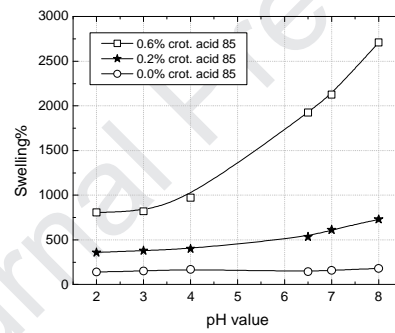
Figure 4: Swelling of the PVP-g-CrA hydrogels at different pH values
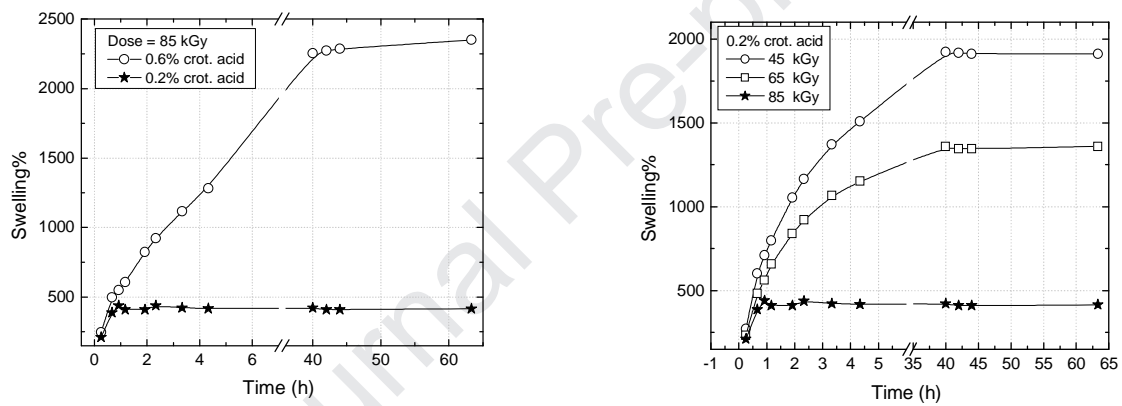
Figure 5 The effect of the CrA concentration (left) and irradiation dose (right) on the maximum swelling of the hydrogels
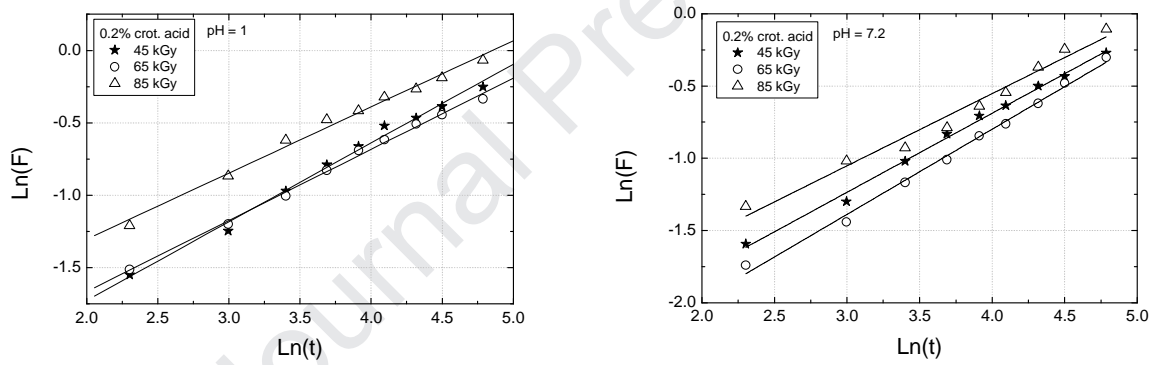
14

Figure 6.   Representation of the fractional swelling of PVP-g-CA prepared at different doses: 45, 65, 85 kGy (0.2% CrA concentration)
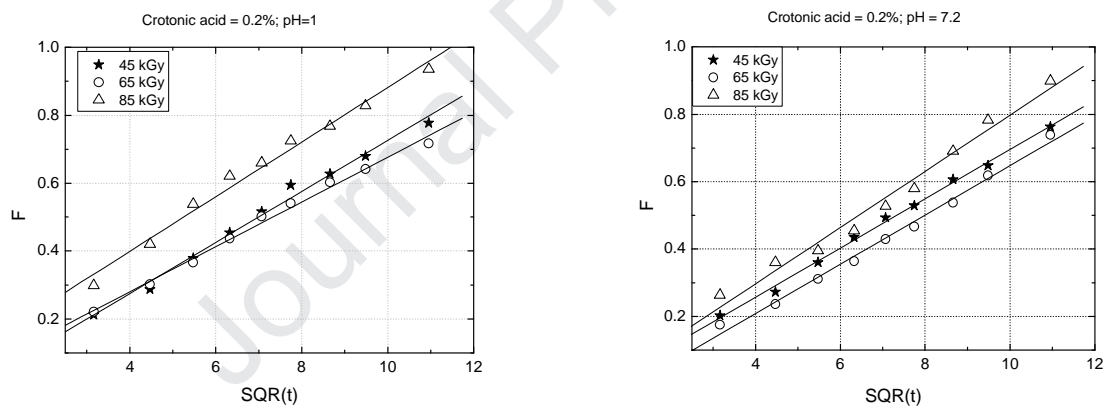
Figure 7: Representation of the fractional swelling (F) of PVP-g-CrA prepared at different doses: 45, 65, 85 kGy (0.2% CrA concentration)
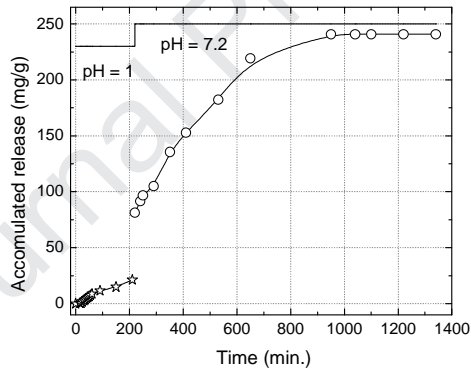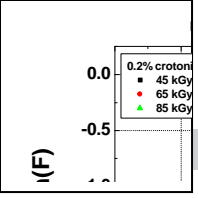
Figure 8. Release profile of ketoprofen from PVP-g-CA in acidic solution (pH 1) for 3.5 h followed by a buffer solution of (pH 7.2) up to 47 h.

Highlights

- PVP grafting with crotonic acid to obtain pH – responsive hydrogels
- Reaction conditions were investigated: irradiation dose and crotonic acid concentration
- The hydrogel system was tested as carrier for ketoprofen
- the release was low in the acidic medium, but better and extended release in the neutral medium
- Possible use as potential drug carrier targeting release in the intestinal medium

Dear Prof. Ulanski

Unfortunately, I could not send my revision to the Journal because of server communication problems (RPC_2018_833_R3).

The comments of the reviewer I have been answered and considered. A small paragraph about polymerization and copolymerization of crotonic acid has been included in the introduction. Page 2 Lines 10-18 as well as the related citation.
I hope that the manuscript is now satisfactory and could be considered for publication in radiation physics and chemistry.

Thanks for your patience and looking forward to hearing from you

Best Regards,

Zaki