Deposition of Ibuprofen crystals on Hydroxypropyl Cellulose/Polyacrylamide Gel: Experimental and mathematic modeling releasing

Claudia Alicia Castillo–Miranda[1], Ana Beatriz Morales–Cepeda[1]*, Carlos Fernando Castro–Guerrero[3], Homero Salas–Papayanopolos[1], Hugo Alberto Ocejo-Velasco[1], Jorge Alberto González–Sánchez[2], Ulises Paramo[1], Hugo De Alva-Salazar[1]

[1] *División de Estudios de Posgrado e Investigación, Instituto Tecnológico de Ciudad Madero, Juventino Rosas y Jesús Urueta s/n, Col. Los Mangos, CP 89318, Cd. Madero, Tamps., México.*

[2] *Departamento de Ciencias Básicas del Instituto Tecnológico de Ciudad Madero, Juventino Rosas y Jesús Urueta s/n, Col. Los Mangos, CP 89318, Cd. Madero, Tamps., México.*

[3] *CONACyT-Instituto de Investigaciones Eléctricas – Reforma 113 Col. Palmira, Cuernavaca, México, C. P. 62490*

Correspondence to: Dr. Ana Beatriz Morales–Cepeda (E-mail: *abmoralesc@itcm.edu.mx*)

ABSTRACT

The crystallization of nonsteroidal anti-inflammatory drug [2-(4-isobutyl-phenyl) propionic acid] ibuprofen (IBP) on a hydroxypropyl cellulose (HPC) and polyacrylamide (PAAm) gel was studied as well as the release kinetics of the drug. The IBP was crystallized on the gel surface of HPC/PAAm, it had a prismatic shape and the growth was made in an aqueous medium, the crystallinity grade of the gel HPC/PAAm and HPC/PAAm-IBU were to 65 and 58. % respectively. The release of IBP is performed by two means: by a non–Fickian diffusion process, and by relaxation of the chains of the gel; without regard of temperature and the diffusion media, this correlates with the lower critical solution temperature (LCST) of the proposed gel. This polymer matrix provides an option for releasing nonsteroidal anti-inflammatory drugs in a temperature range of 35–39°C. Krossmeyer and Peppas mathematical model was simulate for data releases, are statistically significant at 95% confidence level.

KEYWORDS Crystallization, Ibuprofen, gel, Hydroxypropyl Cellulose, Polyacrylamide, mathematic modeling releasing.

INTRODUCTION

Gels represent a major group of biomaterials, they are considered intelligent systems, as they have a swelling response depending upon selective environmental conditions such as pH, temperature, ionic strength, electric and magnetic field, etc [1, 2] .Within the gels we find hydrogels, which are synthesized using water as reacting medium. To achieve selective medium, responsive hydrogels have been synthesized from various homopolymers and copolymers, with recent wider applicability, as monomers combine to provide good mechanical properties, along with other monomers that give gels a hydrophilic material nature, as well as a selective response to environmental conditions.

In recent years, there has been an increased interest on hydrogels, and they have been extensively studied as drug delivery systems that allow the release of the right amount of the active ingredient, at the appropriate time and at specific sites within the body. Previous studies of the HPC/PAAm gels have been performed; the phase behavior has been studied, and it was found that the LCST and UCST (upper critical solution temperature) depend on the amount of HPC. The gel described in this paper has a LCST of 38.3°C and an UCST of 29.1°C.[3]

Several authors reported the simulation of drug releases from delivery system using hydroxypropyl methylcellulose (HPMC) (Siepmann and Pepas, 2001) to elucidate the mass transport and possibility to predict the effect of design parameters tablets.

This research demonstrates that ibuprofen is crystallized on a HPC/PAAm gel and then released. Crystallization is due to the ability of IBP to form the crystals on diamond shape, to stack on the gel due to the solvent, and to the LCST and UCST of the gels. The nosteroidal anti-inflammatory drug (NSAID) release kinetics was studied in two media, buffer saline and

ethanol-water system. The mathematical models were used to find a correlation to experimental data.

EXPERIMENTAL

Materials

In this paper were used hydroxypropyl cellulose (HPC) with average molecular weight (Mw) of ~80,000 g/mol, acrylamide (AAm, purity 97%), methylenebisacrylamide (MBAm, purity 99%), tetramethylethylenediamine (TEMED, purity 99%), ibuprofen (IBP), ammonium persulfate (APS, purity 98%) and divinyl sulfone (DVS, purity 97%), all of them purchased from Sigma–Aldrich. Deionized (DI) water and phosphate buffered solution (PBS) at pH 7.38 was supplied by Hycel.

Synthesis of hydrogels

The synthesis of HPC/PAAm hydrogels was synthesized according to the method of Castro et al.[3] at a ratio of 25/75 wt%. The reaction was carried out in a four-necked flask with a temperature control at 40 ± 1°C and an inert nitrogen atmosphere. The solution consisted of 90 % deionized water and 10% of reagents in the desired amount to work. At the beginning, 1 g of HPC was diluted in 20 mL of DI water, and the mixture was allowed to stir at room temperature for about 15 hours to achieve a homogeneous solution. Then, the reactor was purged with nitrogen and 3 g of AAm were added. Thus, 0.06 g of APS were dissolved with 0.003 g of MBAm in a vial containing 8 mL of DI water, and in another vial containing the same amount of water were dissolved 0.06 g of TEMED; both vials were stirred for 20 minutes. Once well dissolved, the content of first vial was injected in the reactor, then 0.3 mL of DVS was added and finally the second vial was injected in the reactor. The polymerization was done for 1 hour at 40 °C in an inert atmosphere and with constant stirring at pH 7. After the reaction, the solution

was poured in a petri dish, and it was allowed to dry at 40 °C in an oven with vacuum for one week. Once dried, the resulting films were washed with DI water in order to remove the non–reacted substances and then it was left to dry again.

Deposition of IBP

The deposition of IBP on the gel was carried out according to the method of Risbud et al.[4] The NSAID was loaded into the samples by inserting them into an aqueous solution of the drug at a concentration of 5 mg/mL of IBP at room temperature for 48 hours. After this time, the excess of solution was removed from the gels, then frozen at -10°C for 48 hours, and finally allowed to stand at room temperature to constant weight.

Drug release

Once the samples were loaded with the drug, we proceeded to perform the release studies, these studies were done with the dried gel after the incorporation of the NSAID. All of the release experiments were carried out in a heating bath at a controlled temperature (35, 37 and 39 °C) with electromagnetic vibrations (80 cycles/min) using as release means PBS at pH 7.4 and ethanol-water solution (50:50) at pH 7. The release kinetics was measured by taking samples at different intervals of time and determining the drug concentration by UV spectroscopy at wavelengths of 261 nm for samples released in PBS and 255 nm in samples released from ethanol-water solution using a UV-Vis spectrophotometer Perkin-Elmer (model Lambda 10).

Kinetically study of the release of IBP

Release profiles (concentration of drug released versus time) were calculated using absorbance data. The nature of NSAID diffusion from the gels was determined to indicate what model does it fit.

Mathematical models proposed by Higuchi[5], and Korsmeyer and Peppas[6] are among the most widely used to analyze and describe the mechanism by which the release process occurs. Higuchi proposed a mathematical model widely used to describe the empirical process of the drug delivery, which complies with Fick's law and is represented as follows:

$$\frac{M_t}{M_\infty} = kt^{1/2} \quad (1)$$

Where M_t/M_∞ is the released fraction of IBP in a time interval *t*, and *k* is the constant release rate. The mathematical model proposed by Korsmeyer and Peppas is linear for values equal to $M_t/M_\infty < 0.6$. This model attempts to explain release mechanisms where erosion and/or dissolution of the matrix occurs and is a generalized form of the Higuchi Eq. (1),[7] that is expressed as:

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

Where *k* is the release rate constant which incorporates structural and geometric features of the delivery system and *n* is an exponent that indicates the mechanism by which drug release occurs. The exponent value *n* provides information on drug´s kinetics release, so if *n* is equal to 0.5, the drug release occurs through a diffusion phenomenon, Fickian (Higuchi mathematical model) type, if the value of *n* falls between 0.5 and 1, it indicates that the drug release is caused by a non–Fickian mechanism or anomalous diffusion and when *n* equals 1, the mechanism of drug release depends on the process of relaxation of the polymer chains.[1]

The Eq. 2 described the first 60 % of the release behavior of hypothetical distribution; time later Peppas et al. (1987 and 1989) [8-10]; described an empirical equation, for three Fickian diffusional cases. The case II of the Peppas equation´s for Fickian and anomalous release was used in this study[11]:

$$\frac{M_t}{M_\infty} = \frac{2k_0}{C_0\, l}\, t \qquad (3)$$

Characterization of gels

The samples were characterized using Fourier Transform Infrared Spectroscopy (FTIR) in a Perkin Elmer device (model Spectrum One) in attenuated total reflectance (ATR) mode using the frequency range 4000–600 cm^{-1}. Thermal properties were carried out using a Differential Scanning Calorimetry (DSC) in a Perkin Elmer model Pyris 1. The sample was heated from 0°C to 200°C at a rate of 10 °C/min, under a nitrogen atmosphere. Micrographs of the samples were prepared in a Scanning Electronic Microscope (SEM) JEOL model JSM–5900 using a size of sample 1 cm^2; the gels were sputtered with a gold layer. The samples were analyzed with energy dispersive X-ray spectroscopy (EDX), using the EDX instrumentation attached to the SEM, with a Bruker Analyzer operating at 133 eV. X–ray diffraction of the samples was performed with a Bruker AXS D8 Advance diffractometer using CuKα radiation, the samples were cut into squares with sides of 0.5 cm.

Degree of crystallinity was calculated according to the Equation 4 as follow:

$$X_C = \frac{I_{Crystalline}}{I_{Crystalline} + I_{Amorphous}} * 100 \qquad (4)$$

The degree of crystallinity of the gels was calculated by Peak Height method. For cellulosic materials the apparent crystallinity is calculated from the height ratio between the intensity of the crystalline peak (22- 24 ° in 2θ) and the intensity of the non-crystalline material (18° in 2θ).

RESULTS AND DISCUSSION

Infrared spectroscopy

The infrared spectrum of the synthesized xerogel HPC/PAAm is shown in Figure 1c, it can be seen at 3338 cm^{-1} a broad peak attributable to the strong symmetric stretching NH of the PAAm

and the peak at 3182 cm^{-1} is another of high intensity corresponding to the stretch OH in the HPC.[7] Moreover, it is observed the peak at 2929 cm^{-1} of asymmetrical stretching of the CH_3 groups in HPC and a at peak 2867 cm^{-1} due to the symmetric stretching band of CH_2 in the cellulosic derivative.[8] At 1653 cm^{-1} there is a very strong peak attributed to the stretching of carbonyl bond (C=O) in PAAm, with a little peak at 1602 cm^{-1} not so strong due to the bending NH group of the PAAm. The absorption band at 1450 cm^{-1} corresponds to the asymmetric CH_2 (deformation band of the PAAm and HPC). The next peak is the 1408 cm^{-1} attributed to a CH_2 out of plane symmetrical bending. The absorption band at 1271 cm^{-1} was assigned to a CN vibration of PAAm. At 1123 cm^{-1} there is a medium peak attributed to COC stretching and crosslinking reactions.

The spectrum of pure IBP and the gel is shown in Figure 1a and b. The spectrum 1b, in addition to the previously described bands of the gel HPC/PAAm, shows the characteristic peak of the IBP at 1719 cm^{-1}, attributed to the stretching of the carbonyl group C=O (typical of the carboxyl function COOH).[9] The peaks at 3080 cm^{-1} and 770-735 cm^{-1} also indicates that the structure of IBP is present on the sample, and that there is an ortho substitution in the aromatic ring of IBP.

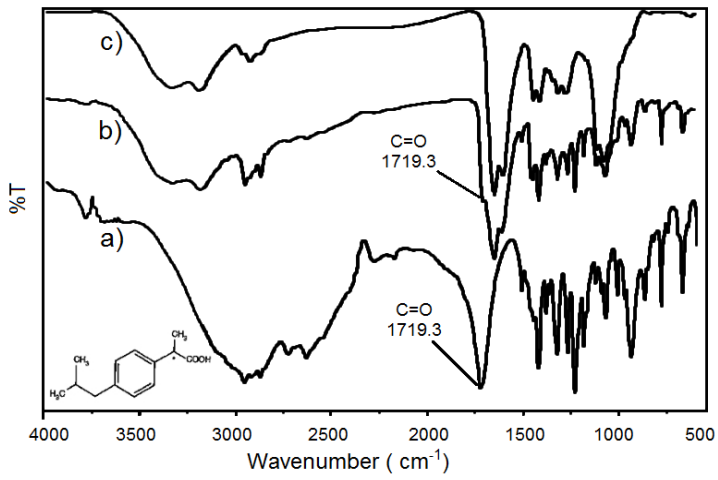

Figure 1. FTIR spectra of a) IBP, b) HPC/PAAM–IBP, c) HPC/PAAm.

Thermal Analysis

De Brandeber et al.[9] showed that ethyl cellulose compatible with IBP has a glass transition temperature (T_g) of about 70 to 80 °C, depending on the amount of cellulose derivative. In Figure 2, the results of DSC analysis are shown. In the curve corresponding to IBP there is a peak around 77 °C, which is characteristic of the active ingredient and corresponds to the melting point of IBP.[11] The curve of the gel with IBP has a peak at 75 °C, this shows that there is a polymer–drug interaction. When there is a single T_g in a composite of two compounds that have its own T_g, then, the system is fully miscible.[10] According to the literature, at 75–76 °C of temperature, the IBP is prismatic and irregular in shape.[12]

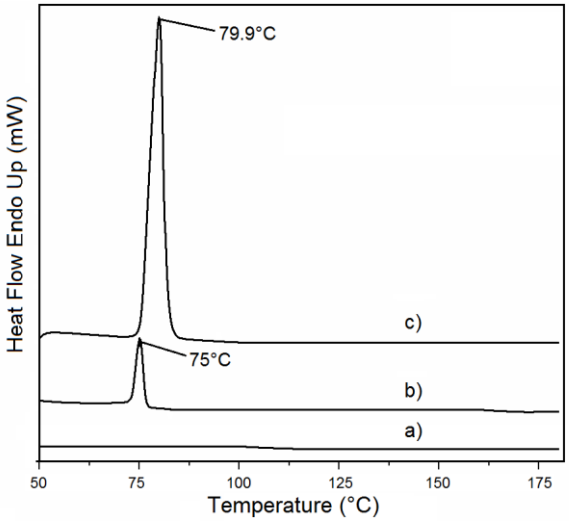

Figure 2. DSC Thermograms of a) HPC/PAAm, b) IBP and c) polymer with IBP.

Morphology and structure

The yellowish appearance in the xerogel (Figure 3) is conferred by PAAm and the swollen gel looks transparent, due to the water incorporated in the matrix.

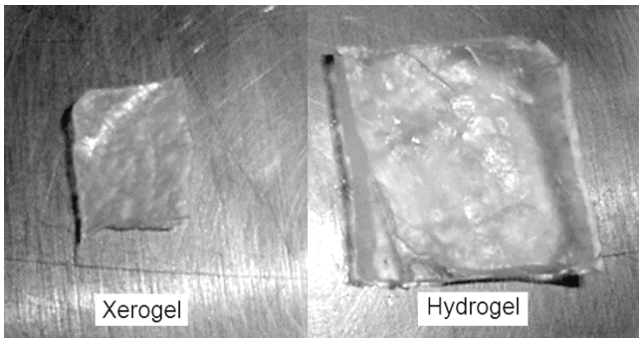

Figure 3. Photographs of the samples: xerogel and hydrogel.

In Figure 4, SEM micrographs of the sample HPC/PAAm are showed at different magnifications (100X and 500X). The pure gel has a smooth and uniform surface without the presence of agglomerates. The uniformity presented by the film indicates that there is no phase separation between the HPC and PAAm. There are pores having 6 μm in diameter; the formation of channels that facilitate migration of solvent is also present.

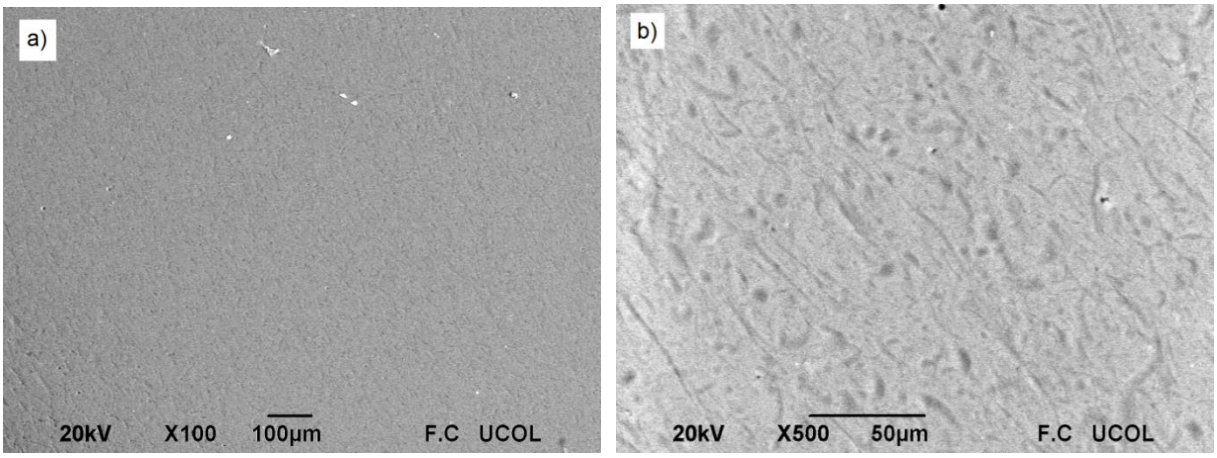

Figure 4. SEM micrographs of the HPC/PAAm xerogel surface at: a) 100X and b) 500X.

Figure 5 corresponds to samples containing pure IBP. The images show a surface with many features, with cuts in different directions and a few shiny white spots that stand out. The sample was compressed and formed a tablet; no crystals are seen.

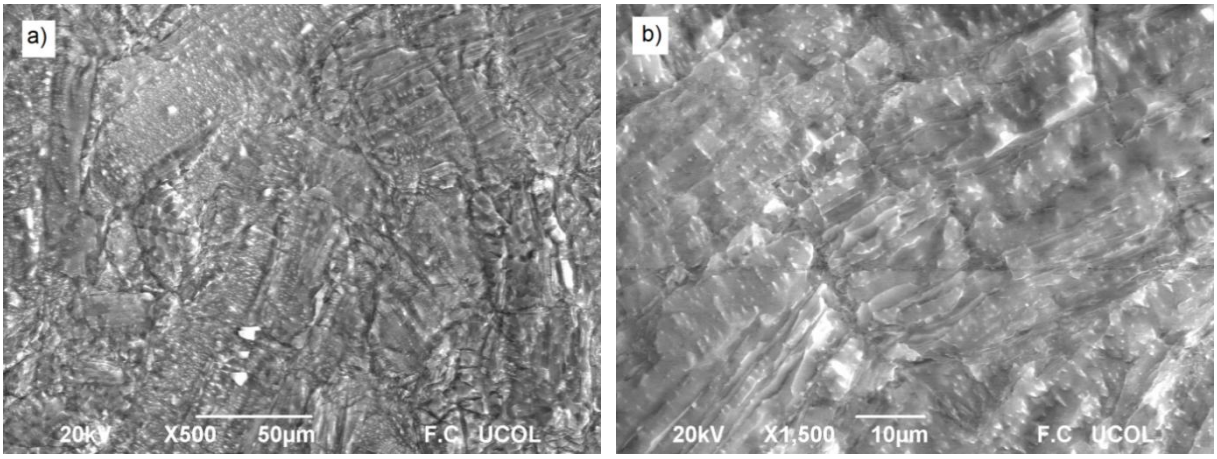

Figure 5. SEM micrographs of the IBP surface: a) 500X b) 1500X.

In Figure 6 are shown SEM micrographs at 100X and 500X of the HPC/PAAm films with IBP incorporated. A surface with a rugged relief is seen in the images, this is due to the inclusion of clusters of various shapes and sizes homogeneously distributed throughout the film; these clusters correspond to crystals of IBP. This corroborates the incorporation of the drug and the existence of a drug-polymer interaction, which was also observed by FTIR spectra and DSC calorimetry. The clusters are shaped in some cases as a diamond with a length of 101.8 μm and they grow vertically with 60 μm, assuming that ibuprofen is adhered to the surface in an average area of 9003 μm^2 (Figure 6a). Like other authors, an induction to crystallization temperature is observed near 40°C, where there is a presence of growth of the crystals in the shape of circles, squares or diamonds.[13] The time of formation of the crystals indicates that after one hour, the crystals have sizes of 100 μm, and they extend from the bottom plane of the gel substrate to the top.

The HPC/PAAm gels are negative thermo–sensitive, because the quantity of polyacrylamide has an influence on the LCST,[14–17] PAAM changes the LCST of HPC, a polymer that is known to have this property.[18]

Figure 7 shows an EDX analysis of the HPC/PAAm pure polymer. The spectrum shows the presence of carbon, oxygen, sodium and sulfur, no nitrogen was detected with the EDX. The quantitative analysis gave, in atomic percentages (at. %), C 51.74 at. %, O 38 at. %, S 9.43 at. %, Na 0.83 at. %. Figure 8 shows an EDX analysis performed on the polymer after absorbing ibuprofen. The analysis detected the presence of nitrogen, but no sodium was detected on the polymer. The composition of the sample with ibuprofen was C 56.92 at. %, O 26.16 at. %, N 16.11 at. %, S 0.81 at. %. Interestingly, sulfur was detected on both samples, APS and DVS both contain sulfur, so, this is the source of S in the samples; the ratio C/S is higher on the sample containing ibuprofen than on the sample of the polymer without the NSAID; this difference is attributed to the presence of IBP, that elevated the content of carbon relative to sulfur.

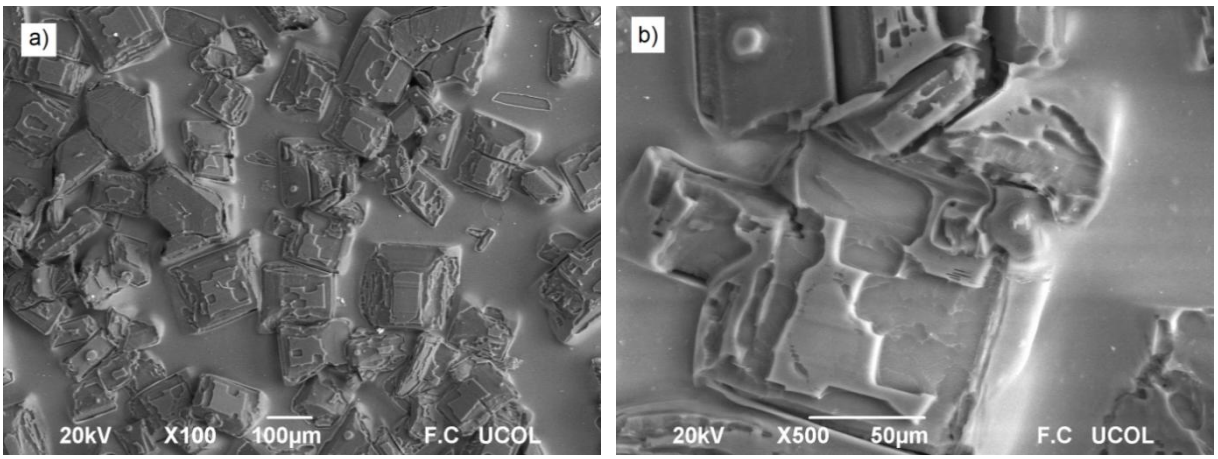

Figure 6. SEM micrographs of the surface of HPC/PAAm films with IBP: a) 100X, b) 500X.

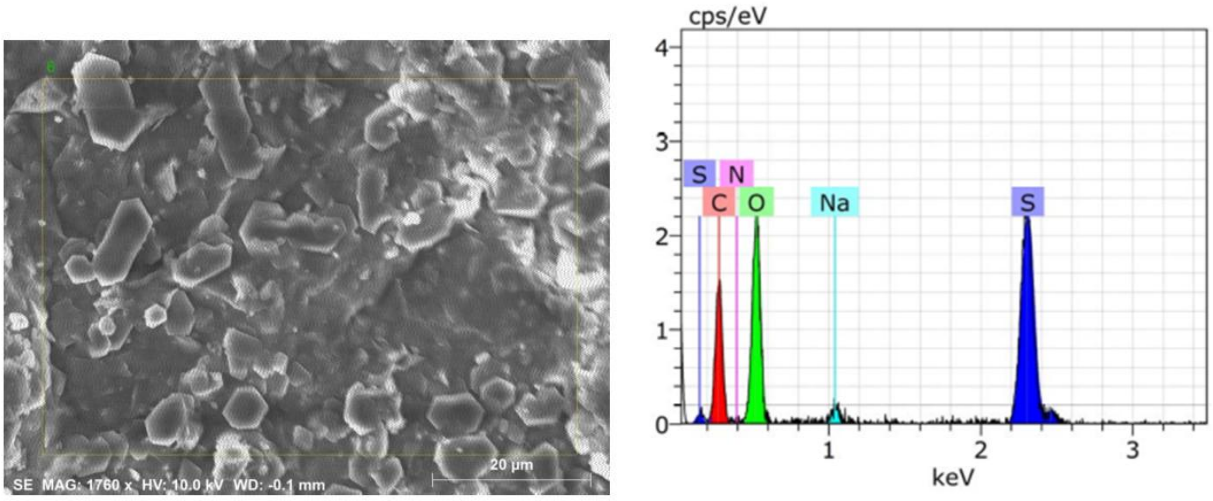

Figure 7. EDX Analysis of the HPC/PAAm xerogel surface.

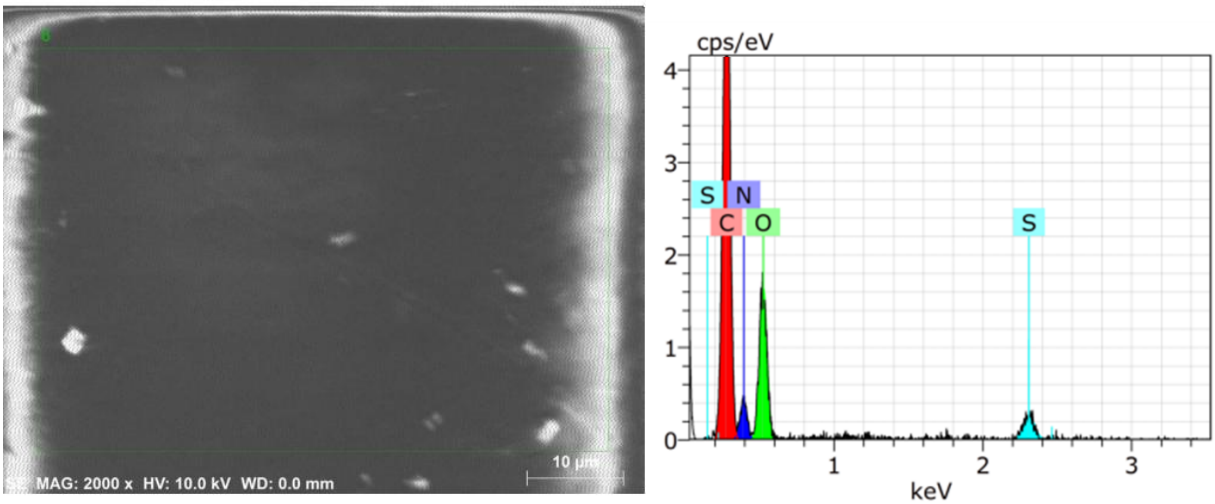

Figure 8. EDX Analysis of the HPC/PAAm with Ibuprofene, xerogel surface.

Drug release

In the PBS solution more IBP is released than in the ethanol-water solution; about 1.17 mg/mL at 35 °C and 0.58 mg/mL at 39 °C in PBS, while in ethanol-water the maximum is 0.45 mg/mL at 39 °C and the minimum is 0.23 mg/mL at 37°C, this suggests that the kinetics of crystallization of ibuprofen on the gel surface is preferred in PBS than in an ethanol-water solution, as various

authors state that it depends on temperature, and temperatures below 40 °C promote super-saturation of ibuprofen.[13]

In order to determine the drug release kinetic model describing the dissolution profile, the software Matlab was used. The simulation of the drug release of ibuprofen in buffer solution (PBS) and ethanol-water solution (EWS) were done using the mathematic models: Zero, first, Higuchi and Korsmeyer-Peppas. ANNOVA results are summarized in Tables 1 and 2 for Zero, First and Higuchi models, and Korsmeyer-Peppas model for both solvents in Table 3. The F-values are not statically significant (Tables 2 and 3). The confidence level is low around 80 %, this demonstrate that the release of IBU is not "zero" and "first order". According to the results of the kinetics of IBP, *n* values are lower than 0.5, this corresponds to the ranges described by the Higuchi model, indicating the existence of several simultaneous processes in the diffusion phenomenon of ibuprofen.[19]

Table 1. ANNOVA data of mathematical models used to ascertain drug release for Buffer solution.

Temperature	Zero order		First order		Higuchi	
(°C)	R^2	F^0	R^2	F^0	R^2	F^0
35	0.5540	0.005	0.439	0.0150	0.67534	0.00063521
37	0.557	0.00503	0.4312	0.0167	0.6898	0.00050198
39	0.764	0.00265	0.6517	0.00167	0.7706	0.00010684

Table 2. ANNOVA data of mathematical models used to ascertain drug release for Ethanol-Water.

Temperature	Zero order		First order		Higuchi	
(°C)	R^2	F^0	R^2	F^0	R^2	F^0
35	0.6924	2.331×10^{-24}	0.3679	1.4299×10^{-6}	0.8579	1.2814×10^{-22}
37	0.63585	6.841×10^{-16}	0.3998	7.4200×10^{-9}	0.80601	1.083×10^{-24}

39	0.54493	$9.202x10^{-13}$	0.308706	$7.685x10^{-7}$	0.7168	$2.060x10^{-19}$

Table 3. ANNOVA data of mathematical model Korsmeyer-Peppas simulation.

Solvent	Temperature (°C)	R^2	F0
Buffer	35	0.86906	0.000052
Buffer	37	0.93486	0.00000314
Buffer	39	0.94927	0.00000115
Ethanol-Water	35	0.79316	$1.3162x10^{-18}$
Ethanol-Water	37	0.823801	$4.9406x10^{-26}$
Ethanol-Water	39	0.745548	$6.6297x10^{-21}$

The first stage of this diffusional process, described by zero, first and Higuchi, the *n* for Fickian diffusion is > 0.5.

For this studies were used for cylindrical samples n = 0.121 and K= 0.477, for the Korsmeyer-Peppas model. The Korsmeyer-Peppas simulation was correlated by ANOVA results for both solvent of IBU medium. From the calculated F^0, it can be inferred that the parameters and the interactions considered in the experimental design are statistically significant at 95 % confidence level. The contribution of Korsmeyer-Peppas simulation shown in Figure 9; in this figure the Korsmeyer-Peppas contribution is shown as an isotherm. It can be observed from Table 3 that the parameter (F) is the most significant factor with 37 °C for both solvents. The best solvent to release the IBP is the buffer solution, using the simulation, the release of ibuprofen at the first 50 minutes is clearly demonstrated. The mathematical model of Korsmeyer-Peppas, is the best correlation between the minimum diffusional exponents.

If we try to correlate the observations from the SEM micrographs, where IBP clusters are seen, there is a threshold of dispersed percolation, and the critical percolation probability is preferred at 39 °C in an ethanol–water solution. The buffer solution releases IBP in smaller quantities without diffusion restriction by polymeric chain relaxation or erosion.

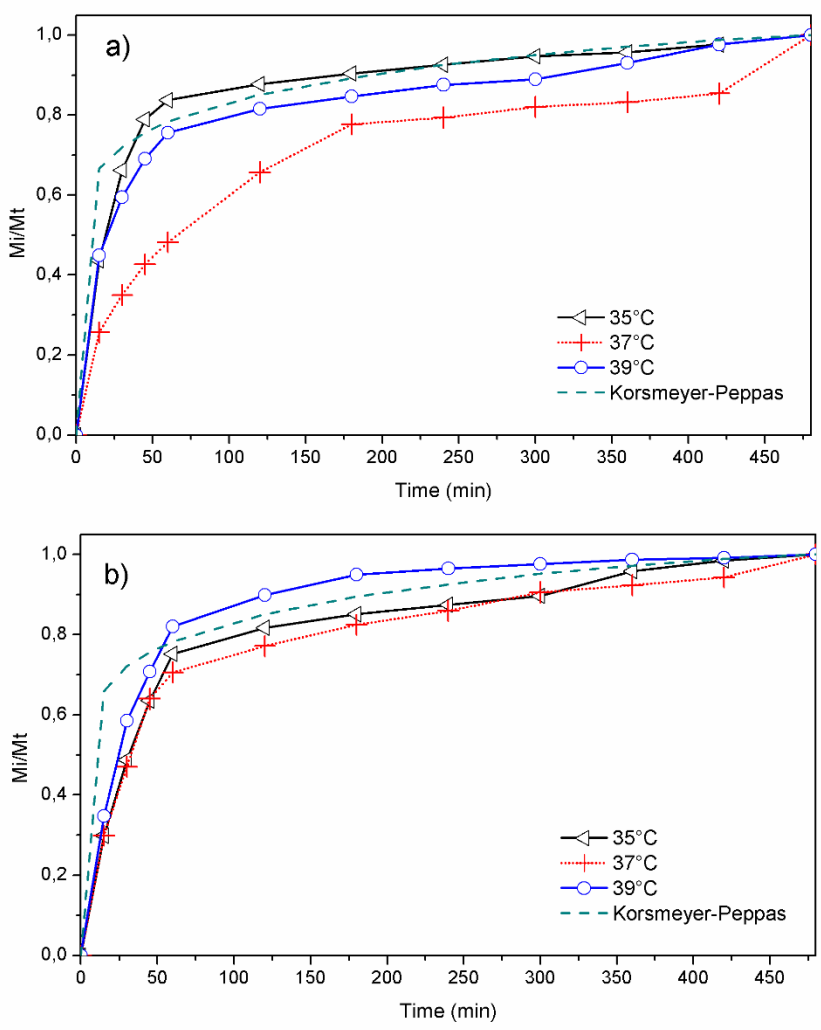

Figure 9. Release of IBP using a) buffer solution and b) ethanol water.

XRD

Figure 10 shows the powder diffractograms of the pure polymer and of the polymer with IBP. The result for pure HPC/PAAm (Figure 10a), is very similar to HPC with a molar substitution (MS) of 4,[20] with reflections of 2θ at 7° and 21°; the material of the diffractogram has a low

degree of crystallinity, as it shows an amorphous halo diffraction pattern,[21] and the sample is noisy, with the peak at 40° being broad and having noise. The diffractogram of the HPC/PAAm gel is shown on Figure 10b; the intensity of the peak at 21° is increased and the sample looks less amorphous; however, the peaks of IBP are not seen on the diffractogram, this indicates that there is a reduction in crystallinity or a change in crystal size because there is a higher quantity of polymers.[22–25]

The crystallization grade of the samples were calculated for the HPC/PAMM gel, having 65% of crystallinity and the sample HPC/PPAm-IBP has 58.6 % of crystallinity, the results are according to reports in literature.[22,23]

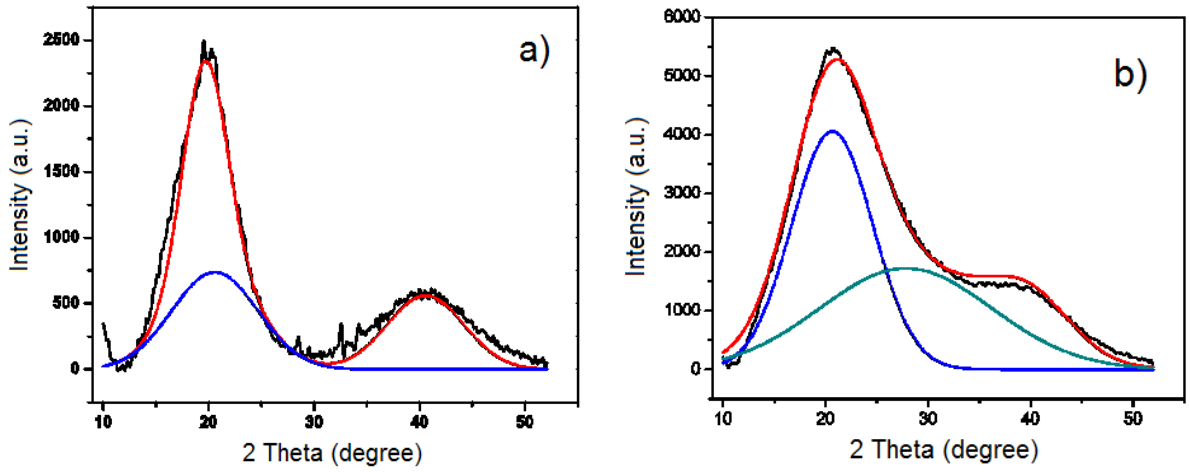

Figure 10. Powder diffractograms of a) HPC/PAAm and b) HPC/PAAm with IBP.

CONCLUSIONS

IBP was incorporated into HPC/PAAm films and the release kinetics was measured. The incorporation of the NSAID was verified with FTIR, the spectra showed that the IBP peaks are present on the films after the incorporation of the drug; this observation was confirmed with the DSC thermograms, which showed a peak at 75–77 °C consistent with the presence of IBP on the polymer. The peak showed by DSC suggested that IBP crystals had a prismatic shape[12] and that

there is a polymer–drug interaction. The SEM micrographs showed the presence of IBP crystals on the surface of the polymer, corroborating the results of FTIR and DSC. EDX indicated a change in the ration C/S in the samples, suggesting the incorporation of a molecule having carbon and no sulfur, as the molecule of ibuprofen. There is a change in the size of the crystals of IBP during the process of incorporation of the NSAID to the polymer, as indicated by XRD.

The HPC/PAAm gel is able to release the IBP that was incorporated in the polymer. The polymer was able to release 1.1 mg/mL of IBP at 35 °C in PBS; the kinetics of the drug release is a non–Fickian phenomenon, in this case, the NSAID is released by a diffusion phenomenon and by viscoelastic relaxation of the polymer during the simultaneous swelling process.[1] Krossmeyer and Peppas mathematical model was simulate for data releases, are statistically significant at 95% confidence level.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest regarding the publication of this article.

ACKNOWLEDGEMENTS

C. Castillo–Miranda and H. Velasco-Ocejo would like to thank SEP and CONACYT (No. 572436) by the scholarship for graduate studies. The authors are grateful to the Mr. D. Pozas Zepeda (University of Colima, Faculty of Science) and R. Morán (National Autonomous University of Mexico, Campus IER Cuernavaca) for the SEM images.

REFERENCES AND NOTES

1. Bajpai, A. K.; Shukla, S. K.; Bhanu, S.; Kankane, S. *Prog. Polym. Sci.* **2008**, *33*, 1088–1118.

2. Chen, X.; Wang, S.; Lu, M.; Chen, Y.; Zhao, L.; Li, W.; Yuan, Q.; Norde, W.; Yuan, L. *Biomacromolecules* **2014**, *15*, 2166–2171.

3. Castro, C.; Morales, A.; Koschella, A.; Heinze, Th. *Macromol. Symp.* **2010**, *296*, 429–435.

4. Risbud, M. V.; Hardikar, A. A.; Bhat, S. V.; Bhonde, R. R. *J. Controlled Rel.* **2000**, *68*, 23–30.

5. Higuchi, T. J. *Pharm. Sci.* **1963**, *52*, 1145–1149.

6. Korsmeyer, R.; Peppas, N. A. In Controlled Release Delivery Systems; Roseman, T. J.; Mansdorf, S. Z., Eds.; Dekker: New York, **1983**, pp 77–90.

7. Mark, J. In Polymer Data Handbook; Oxford University Press: New York, **1999**.

8. Castro–Guerrero, C. F.; Gray, D. G. *Cellulose* **2014**, *21*, 2567–2577.

9. De Brabander, C.; Van den Mooter, G.; Vervaet, C.; Remon, J. P. *J. Pharm. Sci.* **2002**, *91*, 7.

10. Babu, R. J.; Brostow, W.; Kalogeras, I. M.; Sathigari, S. *Mater. Lett.* **2009**, *63*, 2666–2668.

11. Higgins, J. D.; Gilmor, T. P.; Martellucci, S. A.; Bruce, R. D.; Brittain, H. G. In Analytical Profiles of Drug Substances; Academic Press: New York, 2001.

12. Khan, G. M.; Jiabi, Z. *Drug Dev. Ind. Pharm.* **1998**, *24*, 463–471.

13. Rashid, A.; White, E. T.; Howes, T.; Litster, J. D.; Marziano, I. *Chem. Eng. Res. Des.* **2012**, *90*, 158–161.

14. Heiko, J.; Vander, L.; Sebastiaan, H.; Wonter, O.; Piet, B. *Royal Soc. Chem.* **2003**, *28*, 325–331.

15. Hoffman, A. S.; Stayton, P. S.; Bulmus, V.; Chen, G.; Chen, J.; Cheung, C.; Chilkoti, A.; Ding, Z.; Dong, L.; Fong, R.; Lackey, C. A.; Long, C. J.; Miura, M.; Morris, J. E.; Murthy, N.; Nabeshima, Y.; Park, T. G.; Press, O. W.; Shimoboji, T.; Shoemaker, S.; Yang, H. J.; Monji, N.; Nowinski, R. C.; Cole, C. N.; Priest, J. H.; Harris, J. M.; Nakamae, K.; Nishino, T.; Miyata, T. *J. Biomed. Mater. Res. A* **2000**, *52*, 577–586.

16. Qiu, Y.; Park, K. *Adv. Drug Delivery Rev.* **2001**, *53*, 321–339.

17. Cho, S. H.; Jhon, M. S.; Yuk, S. H.; Lee, H. B. *J. Polym. Sci., Part B: Polym. Phys.* **1997**, *35*, 595–598.

18. Werbowyj, R. S.; Gray, D. G. *Macromolecules* **1980**, *13*, 69–73.

19. Lide, D. R. In 76th Edition Handbook of Chemistry and Physics; CRC: Boca Raton, **1995–1996**.

20. Samuels, R. J. *J. Polym. Sci., Part A–2* **1969**, *7*, 1197–1258.

21. Talukder, R.; Reed, C.; Dürig, T.; Hussain, M. *AAPS PharmSciTech.* **2011**, *12*, 1227–1233.

22. Nagpal, M.; Singh, S. K.; Mishra, D. *Int. J. Pharm. Invest.* **2013**, *3*, 88–94.

23. Dalvi, S. V.; Dave, R. N. *Int. J. Pharm.* **2010**, *387*, 172–179.

24. Siepmann J. and Peppas N.A., Adv. Drug Delivery Reviews. **2001**, 48, 139-157

25. Segal, L., Creely, I.J., Martin, A.E. Jr. and Conrad, C.M. **1959**, Textile Research Journal, 29, 786-794.