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Research Article

Mathematical Modelling of Acetaminophen Release in HPC/PAAm Hydrogel: Synthesis and Application

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Hydrogels are commonly used as Drug Delivery Systems (DDS) as patches due to its ability to store drug molecules within their structures. The release can be activated under certain stimuli, such as temperature and pH. In this paper, the mathematical modelling of acetaminophen release in hydroxypropyl cellulose with polyacrylamide (HPC/PAAm) is reported. The HPC/PAAm gel was synthesized in proportions of 25/75 wt% and was characterized by FTIR, DSC, optical microscopy, SEM, and TGA, with and without acetaminophen. The release tests were performed for hypothermic, normal, and febrile human body conditions, at 35, 37, and 39°C, respectively, on two release media: water and phosphate buffer solution. In order to describe the release of acetaminophen in HPC/PAAm gel, a genetic programming algorithm was used to accomplish Multigene Symbolic Regression (MSR). Characterization results showed that the drug was crystallized on the surface of the HPC/PAAm gel. Release test results showed that several simultaneous processes occurred in the acetaminophen diffusion phenomenon. A unique mathematical model was obtained by MSR. This model was able to describe the release of acetaminophen in HPC/PAAm gel with high values of R^2 and adjusted R^2 and to simulate the drug release at times beyond the end of the experiment. High values of R^2 and low values of Coefficient of Variation (CV), Root-Mean-Square Error (RMSE), and Mean Absolute Error (MAE) were obtained from the comparison between the simulated and the experimental data. This allows to conclude that the mathematical model is reliable to represent and simulate the acetaminophen release in HPC/PAAm gel at 35, 37, and 39°C.

1. Introduction

Drug Delivery Systems (DDS) are those transport mechanisms that allow the drug active substances to be released in the human body. Some well-known examples of DDS are pills, capsules, and injections. Nevertheless, the long-term use of pills or capsules may cause damage in the patient's digestive system. Nowadays, several alternatives have been sought, including the use of DDS as patches. How to use the patches is depicted in Figure 1.

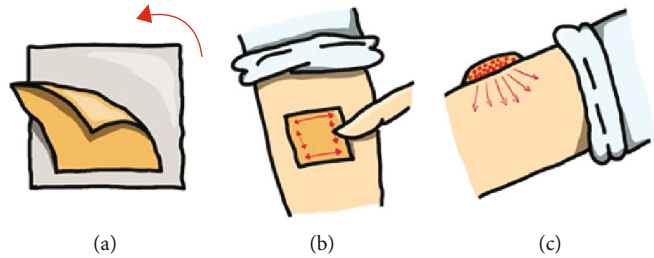

Figure 1: Drug Delivery System as patch: (a) the patch is removed from its protective membrane; (b) the patch is placed on the body; (c) phase of drug release, e.g., the release can be activated by stimuli as temperature or pH.

The patches are commonly made of hydrogels, due to its capacity to store drug molecules within their structures and then release them under certain conditions. Hydrogels are hydrophilic polymers that swell in the presence of a liquid, where the swelling continues until the equilibrium between the cohesive forces of the polymeric network and the osmotic forces originated by the entrance of the liquid into it [1]. The highly porous nature of the hydrogels allows the loading and unloading of drug particles, where the porosity can be adjusted by altering the density of the crosslinks of the polymer network. In addition, the release of hydrogel content may be activated due to environmental stimuli, such as pH or temperature [2]. Therefore, it is important to search for hydrogels capable of releasing drugs at pH and temperature values typically reached by the human body, from 7.35 to 7.45 and from 35 to 39°C (in hypothermic, normal, and febrile human body conditions), respectively.

Currently, numerous scientific researches on hydrogels as Drug Delivery Systems have been reported in [3–22]. Hydroxypropyl cellulose with polyacrylamide (HPC/PAAm) is a particularly interesting hydrogel because it is biodegradable. Castillo-Miranda et al. reported in [3] a study on the crystallization of (RS)-2-(4-isobutylphenyl)propionic acid, a drug commonly known as ibuprofen, within a HPC/PAAm gel, as well as the kinetics of drug release in it. The drug release tests were performed at three temperatures (35, 37, and 39°C) and using two different solvents: a buffer solution of water and phosphate with a pH of 7.38 and a (50 : 50) mixture of ethanol with water with pH 7. The drug release was modelled with the zero-order, first order, Higuchi, and Korsmeyer-Peppas models, represented in Equations (1), (2), (3), and (4), respectively. In most cases, the best adjustments were found with the Korsmeyer-Peppas model, meaning that the drug was released as part of a non-Fickian phenomenon, through the viscoelastic relaxation of the polymer.

The drug release modelling has two main objectives: to understand the phenomenon that governs the release of the drug and to facilitate the design of the drug release devices that will be manufactured and distributed on a large scale commercially. The traditional methods of modelling that are currently used allow to reach only the first objective, but not the second. Among these models, the most widely used are the following [23, 24]:

(1) Zero-order equation:

$$\frac{M_t}{M_\infty} = k_0 t + C_0 \tag{1}$$

(2) First-order equation:

$$\ln\left(1 - \frac{M_t}{M_\infty}\right) = -k_1 t + C_1 \tag{2}$$

(3) Higuchi equation:

$$\frac{M_t}{M_\infty} = k_{\mathrm{H}} t^{1/2} + C_H \tag{3}$$

(4) Korsmeyer-Peppas equation:

$$\frac{M_t}{M_\infty} = k_{\mathrm{KP}} t^n \tag{4}$$

where M_t is the mass of water absorbed in time t and M_∞ is the mass of water in the equilibrium; k_0, k_1, k_{H}, and k_{KP} are the release rate constants which incorporate structural and geometric features of the delivery system; C_0, C_1, and C_H are the intercepts in their equations; and n is an exponent that indicates the mechanism by which drug release occurs.

These models are certainly useful to determine the possible drug release mechanism. Nevertheless, they do not allow the user to make reliable predictions or simulations for drug releasing, e.g., traditional models are not ideal for plotting drug release curves with a limited amount of concentration versus time data.

The present research has two objectives. The first one is to study the incorporation and release of acetaminophen on hydroxypropyl cellulose with polyacrylamide. And the second one is to mathematically model the release of the drug on HPC/PAAm by Multigene Symbolic Regression (MSR). The proposed method can be used to simulate the concentrations of acetaminophen released in HPC/PAAm and to predict the time at which the drug release will be finished.

The rest of this paper is structured as follows: The synthesis of hydroxypropyl cellulose with polyacrylamide as well as

the incorporation of the drug acetaminophen on the HPC/PAAm gel and its characterization are described in the following section. The results of the characterization and the release tests, as well as the details of the mathematical modelling of the acetaminophen release in HPC/PAAm, are reported in Results and Discussion. Finally, the paper closes with a section that summarizes the findings and concludes the paper with a brief discussion on the scope for future work.

2. Materials and Methods

2.1. Materials. For the development of this work the following chemical reagents were used: hydroxypropyl cellulose (HPC), acrylamide (AAm, purity 97%), methylenebisacrylamide (MBAm, purity 99%), tetramethylethylenediamine (TEMED, purity 99%), acetaminophen (PAR), ammonium persulfate (APS, purity 98%), sodium hydroxide (NaOH, purity 97%), and divinyl sulfone (DVS, purity 97%), all of which were purchased from Sigma-Aldrich. Deionized (DI) water and a phosphate buffer solution (PBS) with pH 7.38 were supplied by Hycel.

2.2. Synthesis of HPC/PAAm and Incorporation of Acetaminophen. The HPC/PAAm gel was synthesized according to the method of Castro et al. [25], at a ratio of 25/75 wt%. The reaction was carried out in a four-necked flask with a temperature controlled at 40 ± 1°C and an inert nitrogen atmosphere. The solution consisted of 90% deionized water and 10% 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 stirred at room temperature for about 15 hours to achieve a homogeneous solution. Then, the reactor was purged with nitrogen, and 3 g of AAm was added. Thus, 0.06 g of APS was dissolved with 0.003 g of MBAm in a vial containing 8 mL of DI water, while in another vial containing the same amount of water, 0.06 g of TEMED was dissolved; both vials were stirred for 20 minutes. Once well dissolved, the content of the first vial was injected into the reactor, and 0.3 mL of DVS was added; finally, the second vial was injected into the reactor as well. The polymerization was done for one hour at 40°C in an inert atmosphere and with constant stirring at pH 7. After the reaction was finished, the solution was poured in a petri dish, and it was dried at 40°C in an oven in vacuum for one week. Once dried, the resulting films were washed with DI water in order to remove the unreacted substances, and then, they were left to dry again. Acetaminophen was incorporated into the HPC/PAAm gel by swelling, using solutions of 5 mg/mL of drug in ethanol-water at 50-50 proportion in volume.

2.3. Characterization of the Materials. Fourier transform infrared spectroscopy (FTIR) was performed using a PerkinElmer Spectrum 100 in the range 4500-500 cm^{-1}. Differential Scanning Calorimetry (DSC) was performed from 50 to 200°C. The samples were observed in a ZEIZZ microscope model AX10, in polarized mode, using the software Motic Images Plus 3.0. Micrographs of the samples were obtained in a JEOL Scanning Electronic Microscope (SEM), model JSM-5900, using a size of sample of 1 cm^2; the gels were sputtered with a gold layer. Finally, samples were analyzed with a TA Thermo Gravimetric Analyzer (TGA), model SDT Q600, in the range 30-700°C; data was processed with the software OriginPro 8.6.

2.4. Release Tests. The release tests were performed in deionized water (pH 7) and in a phosphate buffer solution (PBS) with pH 7.38 (in the range of pH values of the human body). Three different temperatures were evaluated: 35, 37, and 39°C (hypothermic, normal, and febrile human body temperatures). Each piece of gel was placed in a container with 5 mL of liquid and remained there for 24 hours subjected to electromagnetic vibrations (80 cycles/minute) and maintaining a constant temperature (35, 37, or 39°C, depending on the case). During the first hour, the PBS was removed and replaced by new liquid at the same temperature every 15 minutes. Subsequently, the PBS was changed once every hour until eight hours is completed. A final change of liquid was also made upon completion of 24 hours of drug release. The drug release was quantified by UV-Vis spectroscopy.

2.5. Mathematical Modelling. The mathematical model that describes the release of acetaminophen in HPC/PAAm was determined by means of the free-access genetic programming tool GPTIPS software in its version 1.0, used to perform Multigene Symbolic Regression in MATLAB [26–28]. The objective of this mathematical modelling was to find a function in the form of Equation (5) to describe the release of acetaminophen over time:

$$y = f(x), \tag{5}$$

where x is the time in minutes and y is the concentration of released acetaminophen in mg/mL.

Experimental measurements of the concentrations of acetaminophen released in mg/mL over time in minutes were used to feed the algorithm. The obtained equation allowed to predict the concentration that would have been released beyond the experiment.

2.5.1. Symbolic Regression. Symbolic regression is an application of genetic programming that finds the best fitting mathematical equation for a data set. This is achieved by generating a random population of mathematical functions in the form of tree structures composed of three parts: a root node, functional nodes, and terminal nodes, as the one shown in Figure 2. The best performing ones are then selected to breeding together in order to generate a new population of functions by means of genetic operators: mutation or crossover, as shown in Figure 3, or direct reproduction (when a tree structure is selected to transfer to the new generation without changes). This process is repeated until the population contains a function that correctly adjusts to the statistical data or until the maximum number of iterations is reached [26–28].

Unlike traditional regression analysis, in which the structure of the model must be specified prior to the fit, SR generates the mathematical function which best fits the available

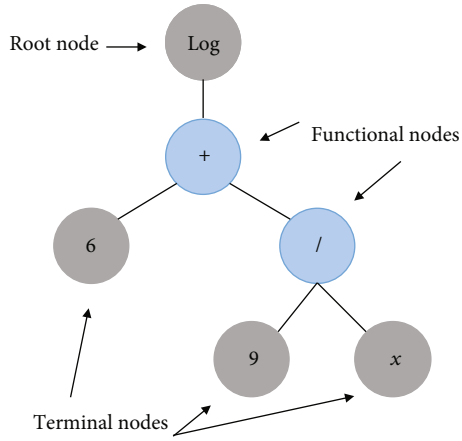

Figure 2: Tree representation of the model $y = \log(6 + 9/x)$.

data by an evolving tree process. Consequently, the main advantage of SR is the possibility of creating structures that include and combine linear, polynomial, potential, logarithmic, exponential, and sinusoidal functions, among many others [26–28].

2.5.2. Multigene Symbolic Regression. Multigene Symbolic Regression (MSR) is an improvement of SR which enables to generate data structures containing several tree structures within. The most typical equation generated by MSR has the form of

$$y = d_0 + d_1 * f(x) + d_2 * g(x), \quad (6)$$

where $f(x)$ and $g(x)$ are functions generated each one by one tree structure. The complexity of the model is controlled by the number of genes G_{max} and the depth of each gene D_{max}, both defined by the user. Each structure generated in the initial population contains a random number of genes (from 1 to G_{max}). For each model, the linear coefficients d_0, d_1, and d_2 are calculated by least squares methods. The best performing ones are then selected to breeding together in order to generate a new population of functions by crossover. In this process, random crossover points are assigned to each structure to breed, and the genes within these crossover points are exchanged with each other. If, after the exchange, the number of genes in a structure exceeds G_{max}, a random set of genes will be eliminated until it reaches G_{max} [28, 29].

3. Results and Discussion

3.1. Characterization of HPC/PAAm. After swelling, an incorporation of 70.03 grams of acetaminophen was achieved for each gram of HPC/PAAm gel. It is to be noticed that the appearance of the HPC/PAAm gel with the incorporated acetaminophen is whitish.

3.1.1. FTIR. In Figure 4, a comparison between the FTIR spectra of HPC/PAAm gel, acetaminophen, and HPC/PAAm gel with incorporated acetaminophen is shown, represented by the blue, black, and red lines, respectively. Acetaminophen shows a signal at 3330 cm^{-1} due to the N-H bond of the amide group, followed by a wide and pronounced peak at 3151 cm^{-1}, which is attributable to the O-H bond of the hydroxyl group. There is also an intense band at 1653 cm^{-1} corresponding to the C=O bond of the amide group; the peaks at 1563, 1505, and 1435 cm^{-1} are due to aromatic vibrations, and finally, peaks at 796-859 cm^{-1} are attributable to the substituted benzene ring in the paraposition.

The HPC/PAAm gel with incorporated acetaminophen has an overlap between the N-H bonds of the amide group and the O-H bonds of the hydroxyl group at 3190 cm^{-1}; these two assignments belong to both the HPC/PAAm gel and the acetaminophen; therefore, an increase in its intensity is appreciated in the HPC/PAAm gel with acetaminophen. HPC/PAAm polymers display the stretching bands of N-H and O-H due to both, the cellulose derivative and the polyacrylamide [25, 30, 31]. At 1653 cm^{-1}, the C=O bond of the amide group is observed. At 1563, 1509, and 1454 cm^{-1}, some aromatic vibrations can be seen. Finally, between 800 and 860 cm^{-1}, the substituted benzene ring in the paraposition is observed. These peaks were previously reported in [32].

The differences between the spectra of acetaminophen and the spectra of HPC/PAAm gel with acetaminophen are observed in as far as amide stretching (3329 cm^{-1} for mono- and 3330 cm^{-1} for ortho-), O-H stretching (3182 cm^{-1} for mono- and 3199 cm^{-1} for ortho-), C=O stretching (1649 cm^{-1} for mono- and 1652 cm^{-1} for ortho-), and C-H symmetric stretching (1506 cm^{-1} for mono- and 1504 cm^{-1} for ortho-). The shifting was also observed for skeletal aryl C-C stretching vibrations (1435 cm^{-1} for mono- and 1442 cm^{-1} for ortho-) and C-N stretching mode vibration (1228 cm^{-1} for mono- and 1220 cm^{-1} for ortho-). The peaks observed at 837, 686, and 601 cm^{-1} for mono- and 837, 686, and 601 cm^{-1} for ortho- are due to out of plane C-H bending (aryl-1, 4 disubstituted). Interestingly, the peaks of the spectra of HPC/PAAm gel with acetaminophen in the range 4000-3500 cm^{-1} differ from that showed in the spectra of acetaminophen; this difference is due to the HPC/PAAm polymer peaks. From this FTIR results, it can be inferred that acetaminophen was correctly incorporated into the HPC/PAAm gel.

3.1.2. DSC. In Figure 5, the DSC thermograms of (a) HPC/PAAm gel and (b) HPC/PAAm gel with incorporated acetaminophen are shown. In the thermogram of the pure HPC/PAAm gel, it is observed that the material does not have any T_g peak. On the other hand, in the thermogram of the HPC/PAAm gel with incorporated acetaminophen, a well-defined exothermic peak at 172°C is observed. In [32], a peak of acetaminophen close to 170°C was reported, which allows us to deduce that the peak in Figure 5 corresponds to acetaminophen. According to [33], fully miscible systems of two compounds present a single T_g, even when each compound in the composite has its own T_g. Similarly, Castillo-Miranda et al. [3] reported a single exothermic peak, corresponding to the melting point of the active substance, in a DSC thermogram of HPC/PAAm gel with incorporated

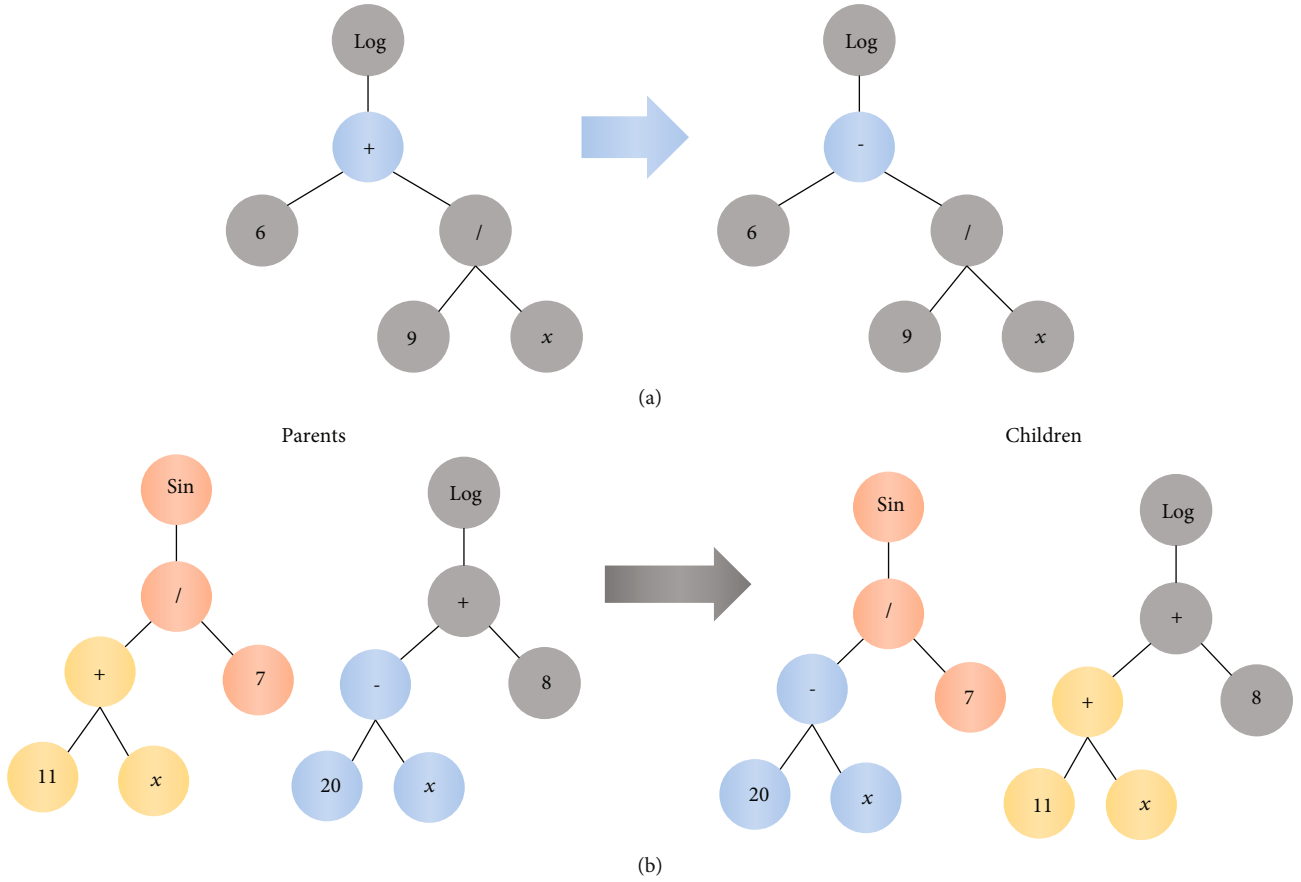

Figure 3: Genetic operators: (a) mutation operation; (b) crossover operation.

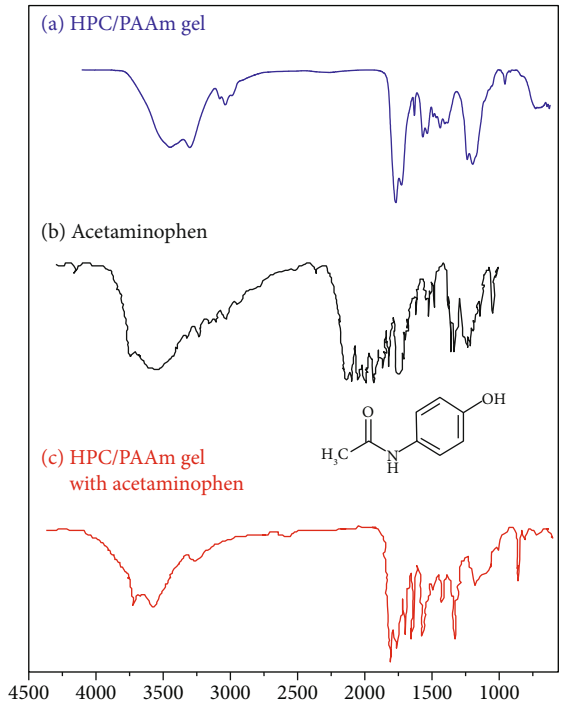

Figure 4: FTIR spectra of (a) HPC/PAAm gel, (b) acetaminophen, and (c) HPC/PAAm gel with incorporated acetaminophen.

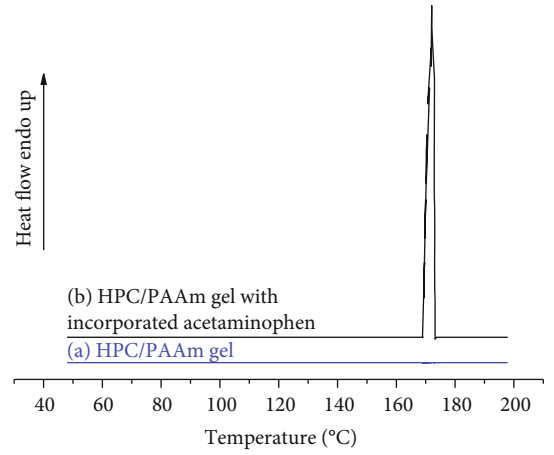

Figure 5: Thermograms of (a) HPC/PAAm gel and (b) HPC/PAAm gel with incorporated acetaminophen.

ibuprofen. This supports the statement that acetaminophen was correctly incorporated into the HPC/PAAm gel, previously established based on the FTIR results.

3.1.3. Optical Microscopy. In Figure 6, the optical micrographs of (a) HPC/PAAm gel, (b) HPC/PAAm gel with acetaminophen, and (c) HPC/PAAm gel with acetaminophen after 24 hours of swelling in water can be observed. All three

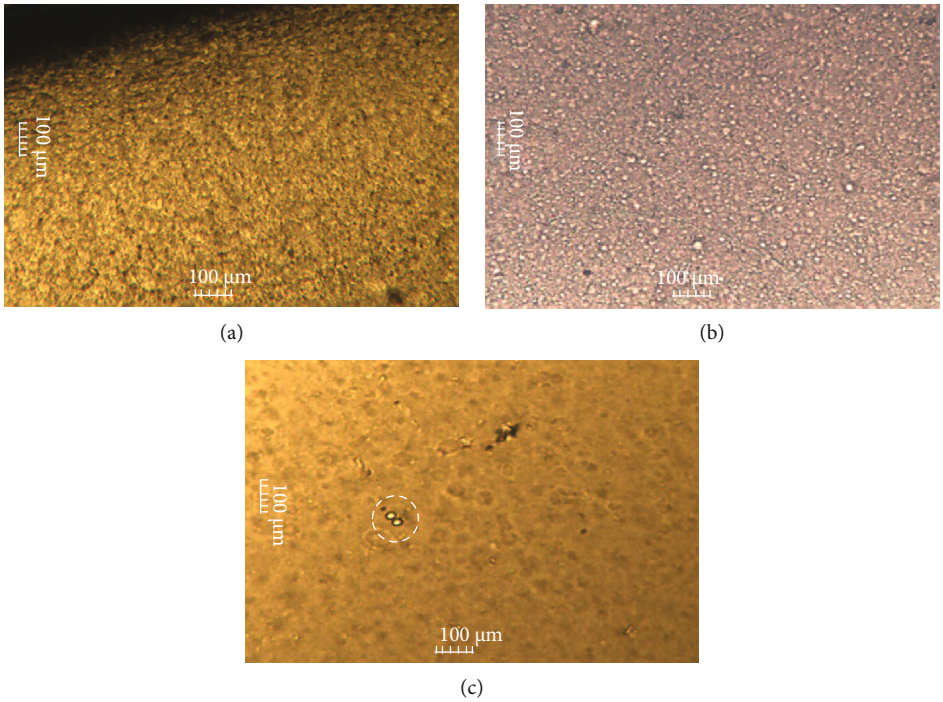

Figure 6: Optical micrographs of (a) HPC/PAAm gel, (b) HPC/PAAm gel with acetaminophen, and (c) HPC/PAAm gel with acetaminophen after 24 hours of swelling in water.

micrographs were taken with 5x and 75° prism opening. In Figure 6(a), the absence of acetaminophen particles in the HPC/PAAm gel is observed. On the other hand, Figure 6(b) shows acetaminophen crystals that are mostly between 3.2 and 6.4 μm in size, although there are some few conglomerates whose size reaches over 15 μm. As it is observed, the said crystals are abundant and well dispersed all over the surface of the HPC/PAAm gel. Finally, in Figure 6(c), it is shown that after 24 hours of swelling in water, most of the acetaminophen particles have been released from the HPC/PAAm gel, observing only two remaining conglomerates of approximately 15 μm each that can be observed within the dotted circle.

3.1.4. SEM. The micrographs of the HPC/PAAm gel with incorporated acetaminophen are shown, at different magnifications, in Figure 7. A homogeneous surface is observed, where the crystals are well distributed on the surface of the HPC/PAAm gel.

Two populations of crystals were seen on the micrographs. One of these consists in rectangular prisms with columnar growth in the {001} plane and a size of approximately 4 μm ($2.1 \times 5.2 \times 1.7$ μm average). The other one consists in irregular prims with columnar growth in the planes {110}, {201}, {001}, and {011} and with no agglomerates, which indicates that the acetaminophen was crystallized on the surface of the HPC/PAAm gel and not between its internal chains. Irregular acetaminophen prisms were also reported in [32]. Besides, other polymers have also presented drug crystallization on the surface. Castillo-Miranda et al. [7] reported the formation of acetylsalicylic acid crystals on the surface of hydroxyethyl cellulose/polyacrylamide gel; they also observed a smooth surface formed by the cellulose derivative. Orthorhombic crystals were also observed on the surface, with larger crystals in the range of 4-10 μm; this morphology is a stable polymorph of acetaminophen at room temperature [34].

Both acetaminophen and the HPC/PAAm gel have atoms that can form hydrogen bonding. Hydrogen bonding between acetaminophen and HPC/PAAm can lead to the formation of not defined crystals, but the formed crystals are stabilized by hydrogen bonding to the polymer surface [35].

3.1.5. TGA. The TGA results are shown in Figure 8. Figure 8(a) shows the weight loss (%) for both the HPC/PAAm gel and the HPC/PAAm gel with incorporated acetaminophen. It can be observed that the thermal behaviour of the drug/polymer system is similar to that of the pure HPC/PAAm gel. The degradation of both materials begins at approximately 225°C, and the final difference between them is approximately 1.4% extra loss of mass when adding acetaminophen to the HPC/PAAm gel. The residual mass was about 18.3% for the pure HPC/PAAm gel and about 16.9% for the HPC/PAAm gel with incorporated acetaminophen. Both curves have also a mass loss of approximately 3% between 175 and 225°C; this loss of mass could be attributed to the decomposition of functional groups on the surface of the HPC/PAAm gel, similarly as explained in [36]. Further, Figure 8(b) shows the derivative thermogravimetric (DTG) curves for both the HPC/PAAm gel and the HPC/PAAm gel with incorporated acetaminophen. It can be observed that the rate of mass loss increased when acetaminophen was added to the HPC/PAAm gel. Also, HPC/PAAm gel peaks moved towards lower temperatures

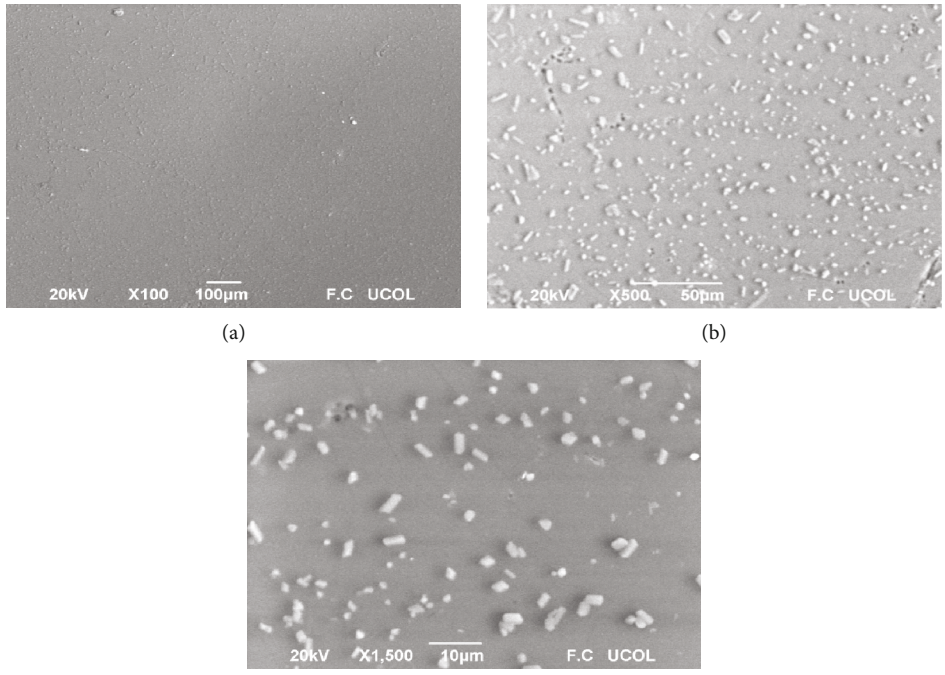

Figure 7: Micrographs of the surface of HPC/PAAm gel with incorporated acetaminophen: (a) 100x, (b) 500x, and (c) 1500x.

when acetaminophen was added. This indicates that the HPC/PAAm gel with incorporated acetaminophen has a lower thermal stability than the pure HPC/PAAm gel, as can be inferred from [37].

From Figure 8 can be observed, besides, that the acetaminophen is stable until some point between 200 and 300°C, and after that, its loss of mass increases rapidly. This was also reported in [32]. Additionally, the thermal degradation for the HPC/PAAm gel is similar to that of the hydroxyproyl methyl cellulose/polyacrylamide polymer, with weight losses due to humidity content and the degradation of the cellulosic polymer at 250°C, while the degradation of the polyacrylate was observed in the 350°C range [38, 39].

3.2. Release Tests. Castillo-Miranda et al. [3] modelled ibuprofen release in HPC/PAAm gel by the traditional methods (Equations (1)–(4)), and the best adjustments were obtained with the Korsmeyer-Peppas model, meaning that the release of drug in HPC/PAAm gel occurred through the viscoelastic relaxation of the polymer, as a non-Fickian phenomenon. Therefore, it was decided to model the acetaminophen release in HPC/PAAm gel with the Korsmeyer-Peppas model, assuming that acetaminophen release would also occur through the viscoelastic relaxation of the polymer, since the hydrogel used as DDS was the same.

The values of the constant rate k and exponent n obtained for the release of acetaminophen in water and in buffer (PBS) from the HPC/PAAm gel by the Korsmeyer-Peppas model, at the three proposed temperatures (35, 37, and 39°C), are presented in Table 1.

From Table 1, it is observed that in all the results the values of n are less than 0.5. Therefore, they do not correspond to any of the intervals described in [40]; this indicates the existence of several simultaneous processes in the phenomenon of acetaminophen diffusion from HPC/PAAm, contrary to the assumption based on [3]. This indicates that the drug to be released from a hydrogel has an influence on the release mechanism.

The concentration of acetaminophen released in the HPC/PAAm gel, with water as the release medium, increased proportionally to the temperature; during the second hour of the release test, at 39°C, the maximum concentration was 0.35 mg/mL. This concentration was also achieved by using buffer as the release medium but at 35°C instead, while the values at 37 and 39°C are a little higher; this indicates that, at the same temperature, a higher release of acetaminophen in HPC/PAAm is obtained by using PBS (pH 7.38) instead of water (pH 7) as the release medium. Therefore, as reported in [4, 5], the pH value has an influence on the release of the drug.

3.3. Mathematical Modelling of the Acetaminophen Release in HPC/PAAm. The time versus concentration data sets obtained from the release tests were mathematically modelled by MSR. A unique equation was obtained by modelling the data sets of the acetaminophen release in HPC/PAAm at 35, 37, and 39°C. Therefore, this equation describes the release of the drug at all of the evaluated temperatures. The used data sets were those of the drug release in PBS (pH 7.38), since this release medium proved to be the most optimal in the release tests. The modelling was carried out using the following configuration of parameters: a tree depth of 5 at

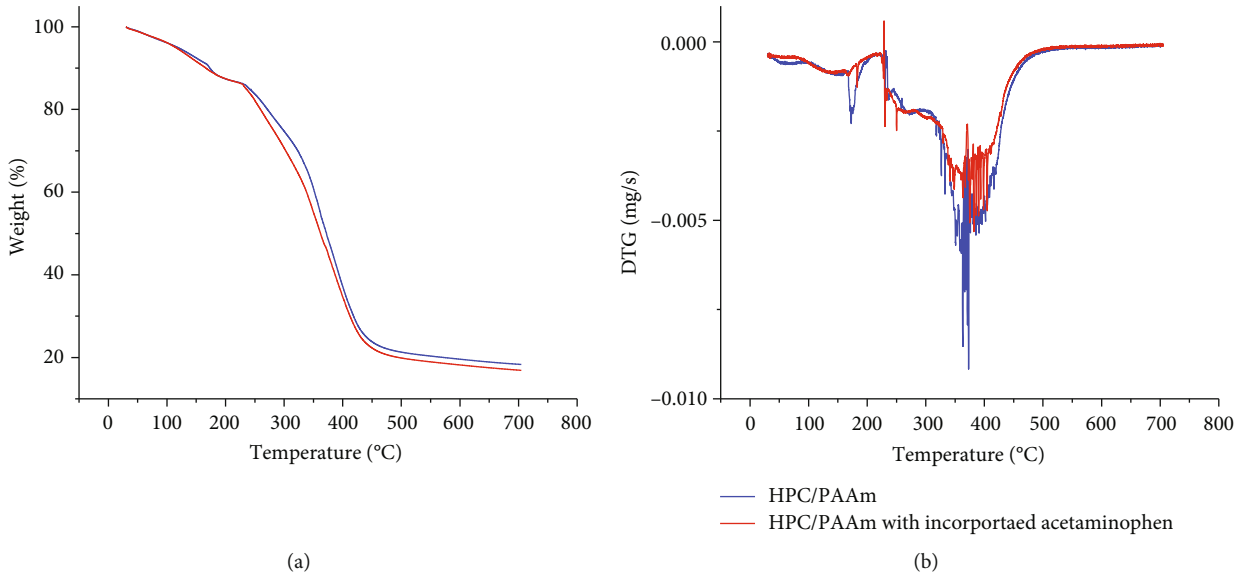

Figure 8: TGA results: (a) TGA curves for HPC/PAAm gel and HPC/PAAm gel with incorporated acetaminophen; (b) DTG curves for HPC/PAAm and HPC/PAAm with incorporated acetaminophen.

Table 1: Values of n obtained for the release of acetaminophen in HPC/PAAm.

Solvent	35°C		37°C		39°C	
	n	k	n	k	n	k
Water	0.1282	0.4913	0.1042	0.5607	0.1277	0.4933
PBS	0.1901	0.3699	0.1400	0.4889	0.1471	0.4623

the beginning of the process, a population size of 100 function trees, and a maximum of 200 iterations. The representative mathematical model for the three experimental temperatures can be described by Equation (7). The coefficients of determination R^2 and adjusted R^2 are calculated as 0.98849 and 0.98795, respectively:

$$y = 26.3 * \tanh\left(\frac{0.2784}{x_1^2}\right) - 0.0003271 * x_1 - \frac{1.559}{\ln(|x_1|)} + 0.7194, \quad (7)$$

where x_1 is the time in minutes and y is the concentration of released acetaminophen in mg/mL.

This mathematical model allows to simulate the concentrations of released acetaminophen even at times beyond the tested and to predict the moment in which the drug release will be finished. Figure 9 shows, in black, the simulation for the release of acetaminophen from HPC/PAAm gel in PBS at any of the three evaluated temperatures, obtained with Equation (7). The red lines in the same figure represent the experimental data at each temperature. As observed, the red curves constructed with experimental data end at about 400 minutes, at which time the experiment finished. However, the mathematical model enabled to predict the release of the drug in times beyond the end of the experiment, allowing to determine that the acetaminophen should be depleted at some point close to 1500 minutes, that is, 25 hours after the start of the release. It is also observed that the simulated data, obtained with Equation (7), resembles the typical kinetic profile of drug release [41].

The simulated data from the mathematical model was compared with the experimental data collected at each evaluated temperature, and the results are shown in Table 2. The listed measures are the coefficient of determination R^2, the Coefficient of Variation (CV), the Root-Mean-Square Error (RMSE), and the Mean Absolute Error (MAE).

As observed, high R^2 values and low CV, RMSE, and MAE values were obtained for the comparisons between the simulated data and the experimental data obtained at all the three evaluated temperatures. These results corroborate that the mathematical model obtained by MSR is reliable to represent the release of acetaminophen in HPC/PAAm gel in PBS at 35, 37, and 39°C. It is also noticeable that the highest R^2 value and lowest CV, RMSE, and MAE values were obtained when comparing the simulated data with the experimental data collected at 35°C. This explains why, in Figure 9, the experimental data of acetaminophen release at 35°C is the most similar to the curve obtained from the simulation and in consequence the most similar to the typical kinetic profile of drug release [41].

4. Conclusions

The samples of HPC/PAAm gel with acetaminophen were characterized by FTIR, DSC, optical microscopy, SEM, and TGA, finding that the drug was correctly incorporated in the HPC/PAAm gel. The correct incorporation of the acetaminophen into the HPC/PAAm gel demonstrates that this material has the potential to be used as a Drug Delivery System as a patch for this active substance. However, it is still necessary to perform more tests to confirm its suitability, including toxicity studies and stability tests; these studies are contemplated as future work.

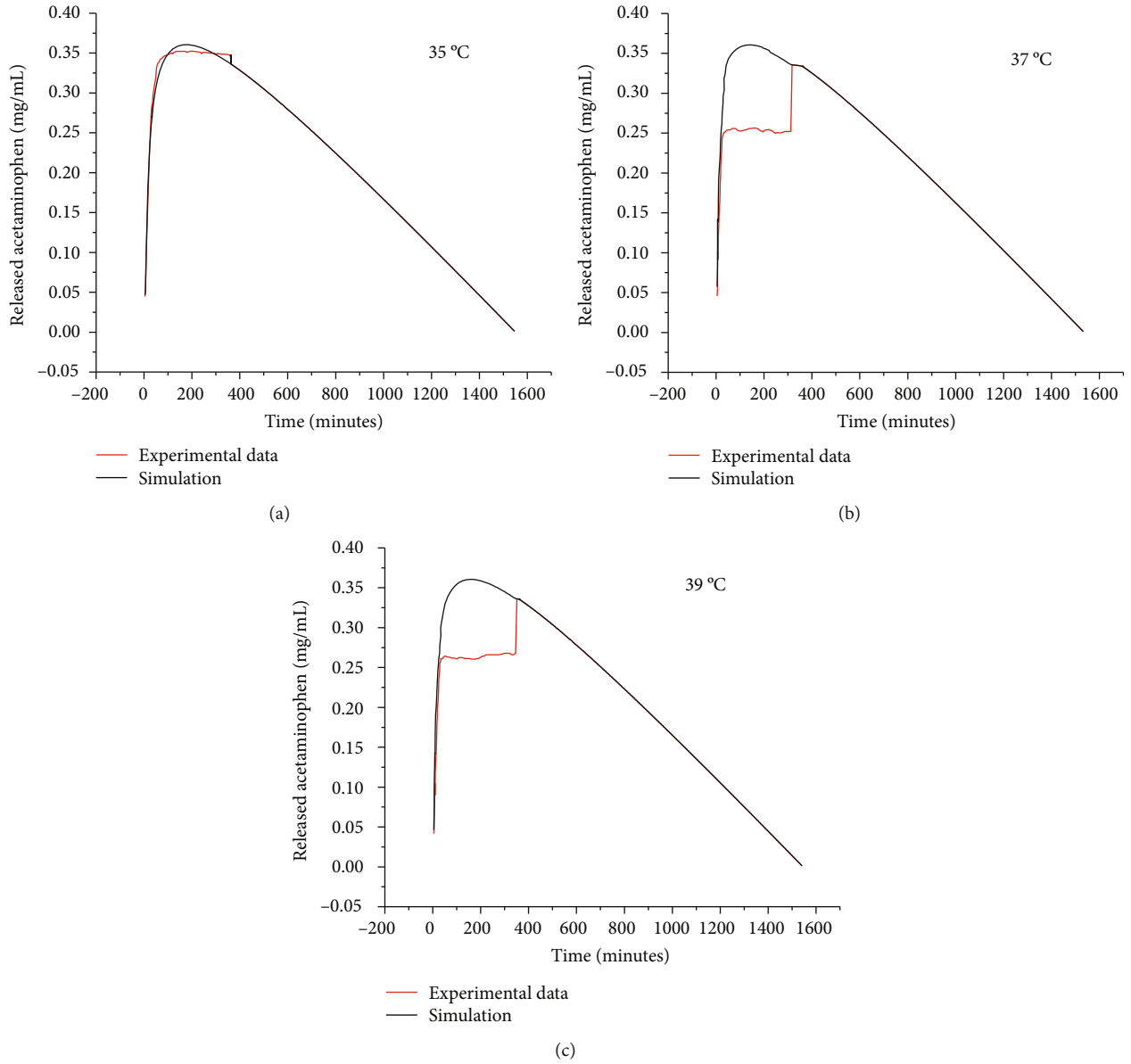

Figure 9: Concentration vs. time curves for the release of acetaminophen from HPC/PAAm gel in PBS at (a) 35, (b) 37, and (c) 39°C.

Release tests were performed in water and in a phosphate buffer solution (PBS) with pH 7.38 at three different temperatures: 35, 37, and 39°C. The release at each temperature was modelled with the Korsmeyer-Peppas model. In all cases, the values of n were less than 0.5, which indicates the existence of several simultaneous processes in the phenomenon of acetaminophen diffusion from HPC/PAAm. Further, the concentration of acetaminophen released in the HPC/PAAm increased proportionally with the pH value of the release medium used.

The results of the release tests were also mathematically modelled by Multigene Symbolic Regression (MSR). The obtained mathematical model achieved R^2 and adjusted R^2 values of 0.98849 and 0.98795, respectively. The equation was used to simulate the concentrations of released acetaminophen in HPC/PAAm at times beyond the tested. It was predicted that drug release would finish 25 hours after its start. The simulated data, obtained with the proposed mathematical model, resembled the typical kinetic profile for drug release. Also, when comparing the simulated data that was generated from the proposed model with the experimental data collected at all the three evaluated temperatures, high values of R^2 and low values of CV, RMSE, and MAE (from 0.9845 to

Table 2: Simulation statistics for the release of acetaminophen from HPC/PAAm gel in PBS at (a) 35, (b) 37, and (c) 39°C.

Temperature	R^2	CV	RMSE	MAE
35°C	0.99982	0.00625	0.00193	0.00736644
37°C	0.99774	0.01987	0.0063	0.08379797
39°C	0.9845	0.0433	0.01366	0.07457

0.99982, from 0.00625 to 0.0433, from 0.00193 to 0.01366, and from 0.00736644 to 0.08379797, respectively) were obtained. The highest R^2 value and lowest CV, RMSE, and MAE values (0.99982, 0.00625, 0.00193, and 0.00736644, respectively) were obtained when comparing the simulated data with the experimental data collected at 35°C.

This way, it can be concluded that the proposed mathematical model is reliable. Moreover, the mathematical modelling by MSR has proven to be an area of opportunity for pharmacological engineers and researchers who are interested in the study of the release of drugs in hydrogels. However, it is important to note that it is still necessary to evaluate the application of the mathematical model that has been presented in this work to model and simulate drug release by using a different drug-gel combination. This is contemplated as future work.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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