Modelling of acetaminophen release from hydroxyethylcellulose/polyacrylamide hydrogel

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Keywords: hydrogel, polymer, drug release, drug delivery system (DDS), mathematical modelling, differential evolution (DE), multigene symbolic regression (MSR)

Abstract

Hydroxyethylcellulose (HEC) is a biodegradable, biocompatible polymer which is responsive to the temperature and pH values that can be reached by the human body. Polyacrylamide (PAAm) is a biocompatible and absorbent material which is highly used as a Drug Delivery System (DDS) due to its swelling capacity. In this work, a composite of HEC and PAAm was synthesized at a ratio of 25/75 wt% in order to evaluate its use as a transdermal DDS for acetaminophen. Drug release tests were performed in a phosphate buffer solution (PBS) at 35, 37, and 39 °C. The Korsmeyer–Peppas model was presented as a mathematical optimization problem and solved by Differential Evolution (DE) algorithm. Additionally, drug release data was modelled by Multigene Symbolic Regression (MSR) based on Genetic Programming (GP) algorithm. A drug release mathematical model was generated by MSR. The model is capable to reliably describe the kinetics of acetaminophen release from HEC/PAAm and to predict the concentrations of drug that is released in times beyond the experiment runtime.

1. Introduction

Transdermal patches offer several advantages over other kinds of Drug Delivery Systems (DDS), like pills or injections. The most important of these advantages are a painless application that does not cause discomfort in the patient’s digestive system, and the gradual release of the drug in a period of about 24 h, reducing the risk of poisoning by overdose [1].

Hydrogels are either chemically or physically crosslinked polymers which are often used in the elaboration of DDS due to its ability to swell upon contact with liquids and to store particles within its structure [2].

The study of drug release from hydrogels made of hydroxypropylcellulose/polyacrylamide [3], chitosan [4], carboxylated cellulose [5], polyacrylamide/sodium alginate [6], silica/polyvinyl alcohol [7], polyvinyl alcohol/chitosan [8], poly(N-vinyl-2-pyrrolidone) [9], methoxy-poly (ethylene glycols)-b-poly (L-lysine)-b-poly (L-valine) [10], poloxamer/chitosan [11], Ag/AgO/carboxymethyl chitosan [12], salecan [13–15], dopamine/hyaluronic acid [16], diacrylate [17] and methacryloyl [18], among others, has been previously reported.

However, only a few hydrogel-based DDSs are currently available for the user [19]. In order to become commercially valuable and reach the market, hydrogels that are developed in the manufacture of DDS must be biodegradable and stimuli-responsive.
Hydrogels whose response is activated under the effect of a certain stimuli such as temperature, pH, solvent composition, mechanical stress or an electric field, among others, are called intelligent hydrogels or smart hydrogels [20]. Smart hydrogels that are biocompatible, biodegradable, and responsive to temperature values of 35 °C–39 °C or to pH values of 7.35–7.45 are ideal materials to be used in the elaboration of transdermal patches, since these are the conditions that can be reached on the surface of the human body. The search for hydrogels that meet all these requirements is still ongoing and relevant [19].

Cellulose is an abundant, natural polymer which can be sustainably synthesized from many forms of agro-industrial wastes through mechanical, chemical or biological methods [21]. As a derivative of cellulose, the hydroxyethylcellulose (HEC) is a biodegradable, biocompatible and intelligent hydrogel. Furthermore, HEC can be easily incorporated with other materials to form composites, due to the high reactivity of its abundant –OH groups. All these characteristics make it a popular material for pharmaceutical usages such as drug delivery [22]. The use of HEC for drug delivery has been reported in previous works [23–25], and composites of HEC with other polymers, for example hyaluronic acid [26] and chitosan [27, 28], have been also applied as DDS. Polycrylamide (PAAm) is also an important absorbent material popularly used as a DDS due to its biocompatibility and swelling capacity [29]. HEC/PAAm hydrogels offer the biodegradability and intelligent response of HEC in combination with the swelling capacity of PAAm. However, there are only two previous reports of HEC/PAAm composites evaluated for its use in drug delivery [30, 31].

The evaluation of any hydrogel as a DDS is an extensive exercise that includes tests of toxicity and cytotoxicity, stability, corrosivity, aerobic metabolism, oxidative and inflammatory reactions and drug release, among others [32, 33]. In this work, we focus on conducting drug release tests and mathematically modelling the results of these.

Drug release tests provide information about the mechanism that governs the drug release from the hydrogel, allowing to classify this mechanism as Fickian, non–Fickian, or pseudo–Fickian. Drug release tests also allow the study of drug release kinetics and the consequent construction of release kinetics curves. Pharmacokinetic parameters such as the peak concentration (C_{max}), the peak time (T_{max}), the terminal half-life (t_{1/2}) and the area under the curve (AUC) can be obtained from these curves [34].

The determination of the type of mechanism that governs drug release can be accomplished with the Korsmeyer–Peppas or Higuchi models, or with the first order or zero-order equations [35, 36]. However, there is still no standardized method to generate mathematical models of drug release from experimental data. It is pertinent to find a method that facilitates and accelerates the study of the kinetics of drug release for each drug-hydrogel system in particular.

In recent years, machine learning techniques such as Neuro-Fuzzy Systems [25] and Artificial Neural Networks [37–39] have been proposed to generate mathematical models that correctly describe the release of drugs from hydrogels. Unfortunately, these methods have the disadvantage of requiring large amounts of experimental data for successful performance [36].

The use of MSR as an alternative for the modelling of drug release from hydrogels has only been reported once [40]. It is still necessary to evaluate the use of MSR in the modelling of drug release from different drug-hydrogel systems, in order to confirm the ideality of the method for this purpose.

In this work, we synthesized a composite of hydroxyethylcellulose and polycrylamide (HEC/PAAm) at a ratio of 25/75 wt%. The hydrogel was loaded with acetaminophen by swelling. Acetaminophen release tests were performed at 35, 37 and 39 °C in a phosphate buffer solution (PBS) with pH 7.38. These temperature and pH values were selected for being in the range of values that can be reached on the surface of the human body.

Acetaminophen release was modelled by the Korsmeyer–Peppas model. The Korsmeyer–Peppas model was presented as an optimization problem and solved by Differential Evolution (DE) algorithm. The results of this modelling allowed to discern that acetaminophen release from HEC/PAAm occurred through a combination of different mechanisms.

Finally, we introduce a novel mathematical model to describe the kinetics of acetaminophen release from HEC/PAAm. This model was obtained by Multigene Symbolic Regression (MSR). The model was successfully applied to simulate the acetaminophen release from HEC/PAAm. The performed simulations made it possible to predict the concentrations of acetaminophen released in times beyond the end of the experiment.

2. Materials and methods

2.1. Materials

The following chemical reagents were used in the development of this work: Hydroxyethylcellulose (HEC), Acrylamide (AAm), Methylenebisacrylamide (MBAm), Tetramethylethylenediamine (TEMED), Ammonium Persulfate (APS), Sodium Hydroxide (NaOH) and Divinyl Sulfone (DVS), with purities of 97%, 97%, 99%, 99%, 98%, 97% and 97%, respectively. All the previously mentioned reagents where purchased from Sigma-Aldrich.
Whereas, the phosphate buffer solution (PBS) was acquired from Hycel. Gaseous nitrogen (N₂), deionized water and N-acetyl-para-aminophenol, also known as acetaminophen or paracetamol, were also required.

2.2. HEC/PAAm preparation, swelling test and drug loading
The HEC/PAAm gels were synthesized in accordance with [31], at a ratio of 25/75 wt%. The synthesis was performed in a four-neck flask. From the start, 1 g of HEC was diluted in 20 ml of deionized water. The solution was stirred at 25 °C for 15 h, until a homogeneous solution was achieved. Then, the reactor was purged with N₂ and three grams of AAm was added to the mixture. Later, 0.06 g of APS and 0.003 g of MBAm were dissolved in a vial with 8 ml of deionized water; meanwhile, in another vial with 8 ml of deionized water, 0.06 g of TEMED were dissolved. The contents of both vials were subjected to stirring for twenty minutes. Once perfectly dissolved, the mixture in the first vial was injected into the reactor with the addition of 0.3 ml of DVS. Later, the mixture in the second vial was also introduced into the reactor. The reaction was carried out for one hour with temperature controlled at 40 ± 1 °C and pH at 7, and an inert nitrogen atmosphere under constant stirring. Once the reaction was finished, the HEC/PAAm was dried at 40 °C for one week and under vacuum conditions. After drying, the xerogel films were washed with deionized water and left to dry again.

The swelling test was performed in PBS. A portion of dry HEC/PAAm, of weight \( W_{fl} \), was collected and placed in a container with 5 ml of the liquid. The weight of the wet material was recorded each 15 min for the first hour, then each hour for the following eight hours, and later once at day until swelling equilibrium was reached. The quantity of liquid that the hydrogel is capable to retain can be mathematically expressed in terms of hydration percentage and swelling degree, as shown in equations (1) and (2), respectively:

\[
W_{C} (%) = \frac{W_{S} - W_{D}}{W_{D}} \times 100 \tag{1}
\]

\[
D_{h} = \frac{W_{S}}{W_{D}} \tag{2}
\]

Where \( W_{C} (%) \) is the hydration percentage, \( W_{D} \) is the weight of the dry material, \( W_{S} \) is the weight of the wet material at the equilibrium and \( D_{h} \) is the maximum swelling degree that can be reached by the hydrogel [41].

The acetaminophen was inserted into the polymer matrix by swelling, with solutions of 5 mg ml⁻¹ in ethanol-water at 50−50 vol%.

2.3. Characterization
Fourier Transform Infrared Spectroscopy (FTIR) analyzes were performed in a Perkin-Elmer equipment, model Spectrum 100, in the 4000–500 cm⁻¹ range. Thermogravimetric Analysis (TGA) were performed with a TA Thermogravimetric Analyzer model SDT Q600, in the 0 °C–800 °C range, with heating rate of 10 °C min⁻¹ and under nitrogen atmosphere. FTIR and TGA data were both processed with the OriginPro 8.6 software. Optical micrographs were obtained with a ZEISS microscope model AX10, in polarized mode, and by means of the Motic Images Plus 3.0 software. Finally, Atomic Force Microscopy (AFM) was performed in a Nanosurf AFM equipment and the resulting micrographs were visualized with Naio control software in its version 3.10.0.

2.4. Drug release tests
The release tests were performed in a phosphate buffer solution (PBS) with pH 7.38 at three different temperatures: 35, 37, and 39 °C. Acetaminophen release occurred in 5 ml of each liquid, for six hours, while the vessel containing the xerogel was being subjected to electromagnetic vibrations of 80 cycles/minute and under a constant temperature. During the first hour, the liquid was removed and replaced every 15 min. Subsequently, the liquid was changed once every hour until the sixth hour. The amount of released drug was quantified by means of UV–vis spectroscopy.

2.5. Modelling of drug release by Korsmeyer–Peppas
The Korsmeyer–Peppas model is a drug release fitting equation that allows to discern the mechanism behind the release of a drug from a hydrogel. This model is represented by equation (3):

\[
\frac{M_t}{M_\infty} = kt^n \tag{3}
\]

Where \( M_t \) is the mass of the water that has been absorbed by time \( t \) and \( M_\infty \) is its mass in the equilibrium, \( k \) is the release rate constant, and \( n \) is the value that suggests what is the drug release mechanism that occurs in a given drug-hydrogel system [35, 36].

The analysis of drug release by Korsmeyer–Peppas requires to find the best fitting of experimental data to equation (3). In order to conduct this analysis, the values of \( n \) and \( k \) must be randomly proposed and then improved by trial and error. However, this method can produce unreliable results.
In the present approach, the $M_r$ is the concentration of released acetaminophen at time $t$ and $M_{\infty}$ is a fixed value, both were obtained from the drug release tests. Whereas, $n$ and $k$ are unknown values that need to be determined.

### 2.5.1. Fitting experimental data by Korsmeyer-Peppas -differential evolution

The Differential Evolution (DE) is an effective and well-known metaheuristic for global optimization [42–44]. The DE is a population-based stochastic search technique for constrained optimization problems. A set of vectors (population) randomly generated are evolved in each iteration by mutation and crossover operators to generate a trial vector.

A comparison between the original-vector and its trial vector is then done to choose the vector which should survive to the next generation [42–44]. This process repeats itself until a stop-criteria is reached and then, the best solution vector is displayed.

The Korsmeyer-Peppas model is presented as an optimization problem as shown in equation (4). Define $\bar{x} = [x_1, x_2] = [k, n]$, the objective problem is as following:

$$
\text{Min } F(\bar{x}) = \frac{\sum_{r=1}^{r_{\text{Max}}} \frac{M_{br}}{M_{\infty}} - x_1 t_r^{x_2}}{r_{\text{Max}}}
$$

(4)

Where, $r_{\text{Max}}$ is the is amount of data, $M_{br}$ is the $r$th concentration of released acetaminophen value at $r$th time. The boundary constraints are defined in equation (5).

The operation of DE can be described as follows:

#### 2.5.1.1. Initialization

A initial population of target vectors are randomly generated by an uniformly distributed number between $[0, 1]$, from the boundary constraints. Each target vectors with dimension $D$ are represented as equation (6).

$$
X_i^G = [x_i^G, x_i^G, ..., x_i^G]
$$

(6)

Where, $G$ is the current generation (iteration) and $i$ is the $i$-th vector, $i = 1,.., N_p$, $N_p$ is the population size. For the present optimization problem $D$ is set to 2.

#### 2.5.1.2. Mutation

The well-know DE/best/1/bin scheme taken from literature is used [43]. The vector $V_i^{G+1}$ is generated for each target vector $X_i^G$ at generation $G$ by equation (7):

$$
V_i^{G+1} = X_{\text{best}}^G + F(X_i^G - X_j^G), \quad r_1 \neq r_2
$$

(7)

Where $F$ is a real-value, it is a scaling factor between 0 and 1, $X_{\text{best}}^G$ is the best vector in generation $G$, and $x_i$ and $x_j$ are randomly chosen indices, $r_1, r_2 \in \{1, 2, \ldots, N_p\}$.

#### 2.5.1.3. Crossover

The binomial crossover was used. The operation is performed between $X_i^G$ and $V_i^G$, they are mixed to yield the trial vector $U_i^G$. The vectors $u_i^G$ in the new population $U_i^G$, using the following scheme, equation (8):

$$
u_i^G =
\begin{cases}
  x_i^G, \text{ rand} \leq Cp & \text{or } j = \text{rand}(i) \\
  x_j^G, \text{ rand} > Cp & \text{and } j = \text{rand}(i)
\end{cases}
$$

(8)

Where $j = 1, 2, \ldots, D$, $Cp$ is the crossover rate factor value between 0 and 1.

Finally, a comparison is made between $X_i^G$ and $U_i^G$ and the vectors with the best fitness values are selected to become a part of the next generation. The process is repeated until reaching the stop-criteria, which is usually a maximum number of iterations.

For this work, the stop-criteria was established as a maximum of 100 iterations (generations) and the population size $N$ was set to 50. DE is implemented in MATLAB R2019b. The computations were carried out on a standard PC (Windows 10, Intel core i7, 2.5 GHz, 16 GB).

### 2.6. Mathematical modelling of drug release by Multigene Symbolic Regression

The data from the drug release tests were modelled by Multigene Symbolic Regression (MSR), in order to find an unique mathematical model to accurately describe the kinetics of acetaminophen release from HEC/PAAm.

The MSR is a tool of Genetic Programming that allows to generate mathematical equations from the modelling of experimental data. This tool offers several advantages when compared to other machine learning approaches.
techniques such as Neuro-Fuzzy Systems or Artificial Neural Networks. The most remarkable of these advantages is the requirement of less data for perform the mathematical modelling [45–48].

Contrary to traditional regression, where only a mathematical model must be provided prior to the modelling of data, the MSR generates a population of random models to be tested. The experimental data are fitted to each of this models and the best equations are saved for the next generation. New models are generated to compete with the previous ones and the process repites itself until a stop criterion is reached. This mechanism allows the user to find the best mathematical model for a determinate set of data.

2.6.1. Operation of the Multigene Symbolic Regression

The Multigene Symbolic Regression (MSR) is an improvement of the Symbolic Regression (SR). Both methods work in a similar way, the main difference is on the complexity of the equations obtained by means of each technique. This difference will be explained in the following paragraphs.

After initialization, a population of random function trees is generated. The population size is configured by the user.

In SR, all the proposed mathematical models are generated from a function tree as the one that is shown in figure 1. The function trees are composed of a root node and several terminal and functional nodes. The reading order is from left to right, starting from the branches until reach the main tree structure.

Experimental data is fitted to each one of the functions and those that provide the best fitness values are saved for the next generation. Then, these will be compared with a new set of randomly generated functions. This procedure is repeated until reaching a stop-criteria set by the user.

In MSR, the mathematical models are generated from tree functions that includes complete functions within its nodes. Therefore, the equations obtained by MSR have the form of equation (9):

$$y = d_0 + d_1 g_1(x) + d_2 g_2(x)$$  \hspace{1cm} (9)

Where $g_1(x)$ and $g_2(x)$ can be all kinds of functions, such as linear polynomial, potential, logarithmic, exponential, and sinusoidal functions, and its combinations; and the linear coefficients $d_0, d_1$, and $d_2$ were calculated by least squares [45–48]. Thus, MSR allows to generate a greater variety of mathematical functions than SR, which increases the possibility of finding the best model to describe a given phenomenon.

2.6.2. Multigene symbolic regression applied to the modelling of acetaminophen release from HEC/PAAm

MSR was performed in MATLAB R2019b through the free-access Genetic Programming Tool GPTIPS software, in its version 1.0 [46–48]. The MSR algorithm was configured to run with the following parameter settings: a tree depth of 5 at the start, a population size of 100 function trees, and maximum of 200 iterations as stop criterion. The concentrations of drug released over time were used to find the best mathematical model to describe the kinetics of acetaminophen release from HEC/PAAm in the form of equation (10):

$$y = f(x)$$  \hspace{1cm} (10)

Where $x$ is the time measured in minutes and $y$ is the concentration of released drug in mg ml$^{-1}$.
3. Results and discussions

3.1. Hydrogel swelling
HEC/PAAm achieved a hydration percentage of 1153%, which is higher than previous values reached by HEC/AAm composites [49]. Besides, our material obtained a swelling degree of 29, which is within the interval of $D_h$ values expected for polyacrylamide-based hydrogels [50].

3.2. Characterization
FTIR spectra of HEC/PAAm, acetaminophen and HEC/PAAm with incorporated acetaminophen are shown in figure 2. The HEC/PAAm spectrum, observed in figure 2(a), exhibits a N-H stretch signal from the amide group at 3330 cm$^{-1}$, as well as stretches C–H of the alkyl group at 3190 and 2920 cm$^{-1}$, all of these signals can be attributed to both hydroxyethylcellulose and polyacrylamide [51–53]. Close to 2850 cm$^{-1}$ there is a small peak that is attributable to the C–H bonds of cyclohexane. At 1653 cm$^{-1}$ there is a C=O bond of the amide group. At 1600 cm$^{-1}$, an N–H bond of the amino group is visualized. Close to 1448 cm$^{-1}$ there is a C–H bend of the alkane group. An O–H bond of the carboxyl group is visible at 1320 cm$^{-1}$. Finally, a C–O stretch bond of the hydroxyl group can be observed at 1120 cm$^{-1}$. In the acetaminophen spectrum, observed in figure 2(b), the signal at 3330 cm$^{-1}$ is due to the N–H bond of the amide group. The thick and pronounced peak at 3151 cm$^{-1}$ is attributable to the O–H bond of the hydroxyl group. The great band at 1653 cm$^{-1}$ corresponds to the C=O bond of the amide group. The peaks at 1563, 1505 and 1435 cm$^{-1}$ are attributed to aromatic vibrations. Close to 1660 cm$^{-1}$, there is an N–H bond of the amino group. At 1465 and 1377 cm$^{-1}$ there are C–H bonds of the alkane group. At 1320 cm$^{-1}$ the O–H bond of the carboxyl group is located. At 1111 and 1050 cm$^{-1}$, C–O stretches of the hydroxyl group are observed. Signals at 960 and 915 cm$^{-1}$ are due to the substituted benzene ring in the para- position. In the spectrum of the xerogel with the incorporated drug, observed in figure 2(c), the signal that was found between 3500 and 3000 cm$^{-1}$ corresponds to a phenolic stretch O–H. The O–H stretches between 3190 and 2920 cm$^{-1}$ are attributable to both the hydroxyethylcellulose and the polycrylamide. Close to 1660 cm$^{-1}$ there is a C=O bond of the amide group. About 1600 cm$^{-1}$ there is a N–H bond of the amino group. Stretches that correspond to a N–O bond were found at 1550 and 1510 cm$^{-1}$, indicating the presence of nitro groups −NO$_2$ in the sample. This will be explained in section 3.2. At 1465 and 1377 cm$^{-1}$ there are C–H bonds of the alkane group. At 1320 cm$^{-1}$ the O–H bond of the carboxyl group is located. At 1111 and 1050 cm$^{-1}$, C–O stretches of the hydroxyl group are observed. Signals at 960 and 915 cm$^{-1}$ are due to C–C bends of the alkene group. Finally, between 800 and

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Figure 2. FTIR spectra of: (a) HEC/PAAm, (b) acetaminophen and (c) HEC/PAAm with incorporated acetaminophen.
860 cm$^{-1}$ are found some peaks that can be attributed to substituted benzene ring in the para- position, in accordance with [54].

The results of Thermogravimetric Analysis (TGA) can be observed in figure 3. In figure 3(a) it is shown the weight loss (%) for both the pure HEC/PAAm and the HEC/PAAm with incorporated acetaminophen. It can be noticed that the thermal behavior of the polymer with incorporated drug is similar to that of the pure polymer; however, thermal degradation of HEC/PAAm begins at approximately 205 °C, while HEC/PAAm with incorporated acetaminophen begins to degrade at a point close to 175 °C. The residual weight is approximately 21.7% for pure HEC/PAAm and approximately 23.7% for HEC/PAAm with acetaminophen incorporated, so the final weight difference is only 2% extra when acetaminophen is added to the HEC/PAAm. On the other hand, figure 3(b) shows the Thermogravimetric Derivative (DTG) curves for both the pure xerogel and the xerogel with incorporated drug. This graph shows the speed of weight loss of both systems and the difference between the thermal stability of pure xerogel and the thermal stability of the xerogel/drug system. It is important to notice that the HEC/PAAm peaks moved towards lower temperatures when the drug was integrated. This indicates that the xerogel with incorporated drug has a lower thermal stability than pure xerogel, as can be concluded from [55].

Moreover, a test of thermal degradation of the pure acetaminophen was also performed by means of TGA in two environments: air and N$_2$. It is observed in figure 4, the drug started to degrade at about 165 °C in both cases, as expected based on [56].

The optical micrographs of the HEC/PAAm gel, the HEC/PAAm gel with integrated acetaminophen and the HEC/PAAm gel after drug release are shown in figure 5. All three micrographs were taken at magnification 5× and with a prism aperture of 75°. In figure 5(a) it can be noticed that the surface of the xerogel is irregular.
even before interacting with the acetaminophen particles. As observed in figure 5(b), no acetaminophen crystals were found on the surface of the HEC/PAAm, contrary to what was expected based on [57]. However, spherical formations between 490 and 630 μm were found, with agglomerations of up to 2435 μm. And, since acetaminophen was detected during drug release tests, it is inferred that such spherical formations contained the drug particles. Besides, as the formations had a spherical shape, it can also be deduced that they contained air as well. Finally, as observed in figure 5(c), after the release tests, the spherical formations increased in size to diameters of approximately 3905 μm, indicating that they swelled with the liquid.

The AFM micrographs of pure HEC/PAAm and HEC/PAAm with incorporated acetaminophen are shown in figure 6. Both micrographs were taken in an area of 25 × 25 μm. In figure 6(a), the previously mentioned spherical-shaped formations can be observed again, by the surface of the pure gel. On the other hand, the micrograph of HEC/PAAm with incorporated drug was taken at a depth between 4.9 and 6.6 μm, so the acetaminophen crystals could be appreciated. An agglomeration of several rectangular, orthorhombic, and irregular acetaminophen prisms can be observed in figure 6(b). These crystal shapes are stable polymorphs of acetaminophen, as established by [58]. The most clearly visible rectangular crystal has a length of 5.5 μm and a diameter of approximately 1.1 μm, which is consistent with the acetaminophen crystal sizes reported in [40].

3.3. Acetaminophen degradation

From the results of the characterization, it can be inferred that acetaminophen reacted after it was loaded into the polymeric matrix. The FTIR analysis showed the presence of a NO2 group in the spectra of the HEC/PAAm with incorporated acetaminophen. This group is not present in the spectra of the pure gel nor in the spectra of the pure drug. This could initially lead to the conclusion that the drug reacted with the polymer; however, it is necessary to consider the presence of air in the spherical formations that contained the drug within the gel, as observed in figures 5(b) and 6(a). Acetaminophen was more likely to react with the immediately surrounding air than with the gel barrier beyond it.

The mechanism of degradation of acetaminophen by oxidation, as mentioned by [59], is shown in figure 7. It is observed that one of the reaction products, the p-nitrophenol, has a NO2 group. Therefore, it can be deduced that acetaminophen was partially degraded by oxidation and that the FTIR results show the presence of at least one of the products from this reaction.

This leads to questioning how the reaction occurred. In [59–62] it is reported that acetaminophen can undergo either electrochemical or photoinduced oxidation when is in the presence of water or aqueous solutions. Air contains water that was trapped alongside the acetaminophen within the spherical formations. The FTIR technique exposes the samples to infrared radiation. This means that the degradation of the drug was probably induced by the operating conditions of this technique.

This also explain why acetaminophen was found and correctly quantified during the drug release tests. Because the tests were carried out in samples that were not exposed to these conditions.
3.4. Drug release modelling by Korsmeyer-Peppas

The Korsmeyer-Peppas model was rewritten as an optimization problem and solved by DE. Table 1 shows the best values that were obtained for exponent $n$ and rate constant $k$.

As observed, the values of $n$ are lower than 0.5 for all the evaluated situations. This indicates that drug release occurred through a combination of Fickian, pseudo-Fickian, and non-Fickian mechanisms [63]. This means that the release of acetaminophen from the HEC/PAAm was influenced both by the diffusion of the liquid and by the viscoelastic relaxation of the matrix, it was also reported in [40].

Figure 5. Optical micrographs of: (a) HEC/PAAm, (b) HEC/PAAm with incorporated acetaminophen and (c) HEC/PAAm after drug release.
3.5. Drug release modelling by multigene symbolic regression

The experimental data from drug release tests were modelled by MSR. The results of all three drug release tests, performed at 35, 37 and 39 °C, were modelled as a single data set. A unique mathematical model was generated

Table 1. Values of $n$ and $k$ for the Korsmeyer-Peppas model applied to acetaminophen release from HEC/PAAm.

|       | 35 °C | 37 °C | 39 °C |
|-------|-------|-------|-------|
| $n$   | 0.2760| 0.3942| 0.0106|
| $k$   | 0.8147| 0.3102| 0.4183|

Figure 6. AFM of: (a) HEC/PAAm and (b) HEC/PAAm with incorporated acetaminophen.

Figure 7. Degradation mechanism from acetaminophen to $p$-nitrophenol.
to represent the acetaminophen release from HEC/PAAm at any of these temperatures. In other words, the equation we propose can be applied to describe the acetaminophen release from HEC/PAAm at any temperature that can be reached by the human body. This model is presented in equation (11):
Table 2. Accuracy of the simulations obtained with the proposed mathematical model.

| Temperature | R²  | CV    | RMSE  | MAE  |
|-------------|-----|-------|-------|------|
| 35 °C       | 0.9994 | 0.0314 | 0.0099 | 0.0389 |
| 37 °C       | 0.9976 | 0.2034 | 0.0960 | 0.0588 |
| 39 °C       | 0.9999 | 0.0062 | 0.0020 | 0.0942 |

\[ y = 0.4807 - 0.0008599 \sin(x_1) - \frac{0.9729}{\ln(|x_1|)} - 0.0002248x_1 \]  

Where \( x_1 \) is the time in minutes and \( y \) is the concentration of released drug in mg ml\(^{-1}\). The global data of acetaminophen release at all the three temperatures was fitted to this model and the results were a \( R^2 \) of 0.9707 and an adjusted \( R^2 \) of 0.9689. This means that the proposed model does accurately represents the release of acetaminophen from HEC/PAAm at any temperature reached by the human body.

The model was used to simulate the release of acetaminophen at each of the three temperatures, separately. Figure 8 displays a comparison between the experimental data recorded at each temperature and the corresponding simulated data obtained by equation (11) for the same time \( (x_1) \) values.

The similarity between a simulation and its experimental counterpart can be quantitatively expressed through the following parameters: Coefficient of Determination \( (R^2) \), Coefficient of Variation \( (CV) \), Root-Mean-Square Error \( (RMSE) \), and Mean Absolute Error \( (MAE) \). The values obtained by each simulation are listed in Table 2.

It is observed that all the \( R^2 \) values are remarkably high and close to one. Moreover, the values of \( CV \), \( RMSE \) and \( MAE \) are, in all cases, low and close to zero. When compared with previously proposed mathematical models for drug release, obtained by methods such as Response Surface Methodology (RSM) and Artificial Neural Networks (ANN), our model obtained higher values of \( R^2 \) [64, 65] and lower values of \( RMSE \) [66]. Thus, it can be concluded that all the simulations that were obtained by means of the proposed mathematical model are reliable.

Additionally, these simulations allowed to predict the concentrations of released drug up to 1500 min (approximately 25 h) after the beginning of the release tests, which only lasted 400 min (6 h). About the minute 1500, the concentrations of acetaminophen displayed by the model began to reach negative values, establishing the point in which the drug would start to deplete. It is relevant to mention that the ideal total time of drug discharge from a transdermal patch is 24 h, by this way the risk of intoxication by overdose is prevented [1]. Therefore, it can be concluded that the model correctly predicted the total time of drug release.

With the results of this work we confirm what is suggested in [40]. Multigene Symbolic Regression (MSR) is a precise method to model drug release from hydrogels. The equations obtained by MSR are able to correctly simulate and predict the release and depletion of a drug for a given drug-gel system. Besides, one single model can be applied to describe the release of drug from the same hydrogel at different temperatures.

4. Conclusions

In this work it was reported the synthesis of HEC/PAAm at a ratio of 25/75 wt% and the incorporation of acetaminophen, by swelling, into the hydrogel. The samples were characterized with FTIR, TGA, Optical Microscopy and AFM in order to confirm the correct incorporation of the drug into the polymeric matrix. The results of the FTIR characterization indicate that a chemical reaction occurred, forming products with nitro functional groups \((-\text{NO}_2\)) . The results of Optical Microscopy characterization showed that acetaminophen was stored into spherical-shaped formations within the gel structure. It was concluded that acetaminophen partially reacted with the water in the surrounding air within these spherical formations, and the reaction that occurred was an oxidation induced by the operating conditions of the FTIR.

Nevertheless, the drug release tests were carried out in different samples that were not previously exposed to radiation nor high temperatures and acetaminophen was correctly quantified in the release medium. Therefore, HEC/PAAm can still be used in the manufacturing of transdermal patches for acetaminophen release, as long as they are stored and transported under proper conditions: in cool places with low lighting. The patient should wear the patch on an area of their body with little to no exposure to solar radiation, preferably under clothing.

Drug release tests were performed in PBS at 35, 37 and 39 °C. The resulting data from these tests were modelled by the Korsmeyer–Peppas equation by means of a Differential Evolution algorithm, finding a combination of Fickian, non–Fickian, and pseudo–Fickian processes intervened in the diffusion of the acetaminophen from the hydrogel.
Additionally, we introduced a novel mathematical model that was generated by Multigene Symbolic Regression. This unique model was obtained from the experimental data of acetaminophen release from HEC/PAAm at 35, 37 and 39 °C. The model allowed us to perform accurate simulations and predictions of acetaminophen release at each temperature and beyond the experimental times. This way, it was demonstrated that MSR is a reliable technique to model drug release from hydrogels.

Further research is still necessary to complement this work. The biocompatibility tests of the HEC/PAAm gel and the characterization of the samples by Dynamic Light Scattering (DLS) are contemplated as future work.

Acknowledgments

The first author acknowledges the support received from Consejo Nacional de Ciencia y Tecnología (Grant No. 591868) to pursue her graduate studies in the academic program of Doctorado en Tecnología Avanzada at Instituto Politécnico Nacional, Centro de Investigación en Ciencia Aplicada y Tecnología Aplicada, Unidad Altamira.

Funding

This project was supported by Instituto Politécnico Nacional (Grants SIP-20195104 and SIP-20200068) and by Tecnológico Nacional de México/Instituto Tecnológico de Ciudad Madero.

Conflicts of interest

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

Code availability

Mathematical modelling with Multigene Symbolic Regression (MSR) was performed in MATLAB by the free-access Genetic Programming tool GPTIPS software, Version 1.0. This code does not belong to the authors of this article. GPTIPS for MATLAB is available for free in: https://sites.google.com/site/gptips4matlab/home.

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