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Research Article

Acetylsalicylic Acid (ASA) on Hydroxyethylcellulose/Polyacrylamide Gel (HEC/PAAm) as a Proposal for a Dermatological Compress: Mathematical Modeling of ASA Release Kinetics

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Currently, acne in adolescents and adults is caused by an infection in follicles caused by hormonal changes, stress, water pollution, air, and earth; the last one comes into contact with the skin through the hands of patients. This project presents the incorporation of acetylsalicylic acid (ASA) to the hydroxyethylcellulose/polyacrylamide gel (HEC/PAAm) in the synthesis of gel or by its swelling. The results show us that the incorporation of ASA is possible by both methods; first, the incorporation by synthesis of degradation of the gel is more visible. The infrared spectroscopic analysis shows the functional groups of gel and ASA, 2921 and 2863 cm^{-1}, whose assignments correspond to CH_3 and CH_2 groups, which are part of both the polymer and the ASA molecule, which confirms the interaction between the two groups. The microscopy photographs (SEM) show on the surface the drug in irregular whitish orthorhombic forms due to swelling; arborescent structures are observed in the case of the incorporation of the ASA drug by synthesis. Swelling kinetics has a Fickian form. The Higuchi model conforms to the release of ASA because the level of confidence is 90%. This gel was allowed to release 0.35 mg/hour, thus allowing the patient to have a continuous form of the release, in the affected area in a short period of time.

1. Introduction

Acne is an inflammation of the follicles, due to the obstruction of sebaceous glands and hormonal changes (in adolescence or in adulthood); a statistic published in the year 2017 shows that 9.4% of the world population suffers from acne [1]. Depending on the degree of progress of acne, it goes from a teenage acne, rosacea, hormonal, with nodules, with cysts, severe. These types of acne cause psychological problems resulting in social segregation in adolescents and adults, this is because their possibilities of professional, work and personal growth (search for a partner, friendships) are affected, causing depression and low self-esteem [2].

Treatments to control or diminish acne go from washing the face and/or affected zones (back, chin, and neck), hand-washing, avoiding sun exposure, and applying ointments and astringent lotions, with benzoyl peroxide, acetylsalicylic acid, and antibiotics such as erythromycin and in severe cases isotretinoin; if it is hormonal-type acne, it should be treated with appropriate hormonal medications.

On the other hand, the release of drugs used in the last decades in body temperature control, contraceptive patches, the version of medications for the control of muscle pain, cancer, bones, as a palliative. These patches are based on gels where the drug is deposited for controlled release or for stimuli such as changes in body temperature or change of pH if ingested.

In general, hydrogels that present a critical temperature of higher miscibility (UCST (upper critical solution temperature)) expand as temperature increases, while those with an LCST contract. The LCST of a polymer can be varied by copolymerizing it with monomers with different degrees of hydrophilicity [3]. Hydrogels sensitive to temperature changes are characterized by having a critical temperature of lower miscibility (LCST (lower critical solution temperature)) of the polymer or copolymer in aqueous solution.

In essence, certain polymers with an appropriate cross-linking composition and density can swell greatly in water at room temperature and collapse to the LCST. Acetylsalicylic acid or ASA is a nonsteroidal anti-inflammatory drug (NSAID) of the family of salicylates, frequently used as an anti-inflammatory, analgesic for the relief of mild and moderate pain, and antipyretic for the reduction of fever and as an antiplatelet drug indicated for people at high risk of blood coagulation, mainly individuals who have already had an acute myocardial infarction. The adverse effects of aspirin are mainly gastrointestinal, that is, gastric ulcers and stomach bleeding, mainly when administered orally.

The incorporation of nonsteroidal drugs in gels for prolonged release is one of the options for patients with gastrointestinal problems. The incorporation of drugs such as ibuprofen on hydroxyethylcellulose gels has been studied as an option [4] where the capacity of HEC as a biodegradable and biocompatible gel was investigated, incorporating the drug by swelling, achieving the incorporation of 5 wt% of the drug.

Kalagasidis Krušić et al. [5] prepared copolymer hydrogels of N-isopropylacrylamide acid (PNIPAM) and itaconic acid (IA), crisscrossed with MBAAm by radical copolymerization, and investigated the composition ratios to find materials with good swelling and drug release properties. Paracetamol was used as a model drug, incorporating it by swelling in xerogels in aqueous solution of drug (10 mg/mL) at room temperature for 2 days. It was found that the swelling behavior of the investigated hydrogels depends on pH and temperature with limited swelling and the lowest degree of swelling is at lower pH values and temperatures above the LCST value of PNIPAM (around 34°C). The presence of "IA" incorporated into the network weakened the shear strength of the hydrogels. The pore size was calculated for the different PNIPAM/IA compositions, which range from 0.019 to 0.041 μm, which is why they are considered as microporous. On the other hand, paracetamol was released after 6 hours at pH 2.2 and after 2 hours at pH 6.8. In all the experiments, the drug was released in the first five hours. The values of the diffusion exponent indicated a release kinetics of Fickian paracetamol. According to the results obtained, the swelling behavior, mechanical properties, drug loading capacity, and drug release rate can be controlled by the hydrogel cross-linking composition and density, which is important for the application of hydrogels investigated as drug release systems.

In MojtabaTaghizadeh and Javan [6], a nanoparticulate, biocompatible, and biodegradable drug release system was prepared to increase the efficiency and bioavailability of oral drugs. They prepared, by the emulsion method, nanoparticles of chitosan containing salicylic acid. The morphology of the nanoparticles was characterized by SEM, and the particle size distribution was examined by laser light scattering. The release of the drug and the content was examined by UV spectroscopy using phosphate buffer at pH 7.4 and at 37°C. The effects of the different initial loads of the drug on the content and its release were investigated. The nanoparticles were spherical and their average size was 300 nm, and the content of the drug was in the range 20-35%. All nanoparticles have an initial release and a release behavior that better fits the Higuchi model. The release of salicylic acid from the chitosan nanoparticles was Fickian.

The synthesis of HEC/PAAm has been previously studied by Alonso et al. [7], by means of free radicals using potassium persulfate (KPS), demonstrating the dependence of pH and temperature on the swelling of gels. The gels showed a maximum swelling of 1200 wt%, at a temperature of 30°C, decreasing when the temperature and amount of HEC in the gel matrix increased.

Acetylsalicylic acid in gels is potentially accepted in the pharmaceutical industry in the treatment of dermatological problems, such as acne in adolescents and/or adults, and the exposure of acetylsalicylic acid in soaps, ointments, lotions, exfoliants, and emulsions, where they incorporated from 1 to 40 wt% of ASA, in cellulose gel with the help of isopropyl alcohol [8].

Castillo-Miranda et al. [9] investigated the mathematical model of Higuchi in the release of ibuprofen on the HPC/PAAm gel, in two solutions in the buffer and in saline, finding that this release is possible to predict at an average temperature between 36 and 39°C. In addition, it was found that ibuprofen crystallizes on the surface, due to the method of incorporation of the drug by swelling.

In the present investigation, we present the simulation of three mathematical models for the kinetics of drug release and nonsteroids such as acetylsalicylic acid (ASA), on the hydroxyethylcellulose/polyacrylamide gel (HEC/PAAm). Research was done to find the best way to investigate the incorporation of ASA into the proposed gel, and this was analyzed by infrared spectroscopy, X-ray, DSC, and DMA, to ensure that ASA does not degrade and is found in the gel.

2. Methodology

2-Hydroxyethyl cellulose (HEC) was obtained from Sigma-Aldrich, the viscosity (in water at 2% weight) of which is 4500 to 6500 cP. Its degree of substitution is 1.5, and the degree of molar substitution is 2.5. Other chemicals used in this study were as follows: acrylamide (AAm), 2-propenamide (C_3H_5NO, Sigma-Aldrich brand with 97% purity), ammonium persulfate (APS), $(NH_4)_2S_2O_8$ (the initiator of the polymerization of acrylates via free radicals, Sigma-Aldrich brand

with 98% purity), methylenebisacrylamide (MBAm), N,N′,-methylenebis(2-propenamide), $C_7H_{10}O_2N_2$ (cross-linker for polyacrylamide, Sigma-Aldrich brand with a purity of 99%), N,N,N′,N′,-tetramethylethylenediamine (TEMED), 1,2-di(dimethylamino)ethane, $C_6H_{16}N_2$ (co-catalyst for the formation of free radicals of APS, Sigma-Aldrich brand with 99% purity), and sodium hydroxide (NaOH; used at 1.0 M in deionized water to regulate the reaction at pH 12; Sigma-Aldrich brand with a minimum purity of 97%).

The buffer solution was a phosphate solution, pH 7.384 ± 0.003 at 37°C, and was obtained by HYCEL brand. The acetylsalicylic acid ($C_9H_8O_4$) was obtained by Sigma brand, 99% purity.

2.1. Synthesis of Gel Ratio 25/75 wt% [10]. The reaction was carried out in a four-neck flask with a temperature control medium at 40°C ± 1°C and an inert atmosphere with nitrogen. The solution consisted of 95% deionized water and 5% reagents in the desired amount to work. For the 50/50 ratio, 27.5 mL of deionized water was added, swept with nitrogen, and 1.875 g of AAm was added, which is in constant agitation while the temperature was increased to 40°C. In a vial with 10 mL of deionized water, 0.0375 g of APS was dissolved together with 0.0019 g of MBAm, and in another vial with the same amount of water, 0.0375 g of TEMED was dissolved. When the temperature was 40°C, HEC was added to the reactor, the first vial was immediately injected, and then the second vial with TEMED and then 0.19 mL of DVS was injected, all in an inert atmosphere. At the end, about 1 mL of 1.0 M NaOH was added and the pH of the solution was checked, which was 12. The reaction lasted 30 minutes; once the reaction was finished, it was allowed to dry at 40°C in an oven in a vacuum for a week. Once the film was dry, the gel was rinsed with deionized water and dried.

Standard solutions of the drug containing 5 mg/mL were prepared in the solvent (phosphate buffer, ethanol-water 50 vol%).

The synthesis of the gels was reported by Castro-Guerrero, where the amount of HEC, PAAm, and cross-linker was observed, observing that at a high level of divinyl sulfone (DVS, cross-linking), the network is more cross-linked and rigid, having agglomerates of particles of the smallest gels. Castro varied the amount of the cross-linker based on 0.18 g of DVS/g of polymer [11]; however, this is different from the effect of the pH in the network, and the alkaline pH catalyzes the cross-linking between the DVS and the cellulose derivative, which increases the percentage of swelling by preventing the gel from being diluted. This is based on the synthesis proposed by Castro (thesis), and as a cross-linker base of 0.18 g of DVS/g of the polymer.

2.2. Incorporation of Drugs by Swelling. The incorporation of the drug to the gels was according to what was reported by Kenawy et al. [12]; once the drug solutions were prepared, pieces of xerogels were cut and weighed, and their thickness was measured. The gels were immersed in a solution with the drug for 48 hours at room temperature; at the end of this time, the gels were removed, and the excess solution was removed and weighed. Subsequently, they were frozen at −10°C for 48 hours, then allowed to stand at room temperature until constant weight [13].

With the maximum amount of solution absorbed by the gel, the amount of drug theoretically absorbed is calculated. According to Makino et al. [14], the amount of drug inside the gel is equal to the solution incorporated in the drug.

2.3. Incorporation of the Drug by Synthesis. The drug acetylsalicylic acid (ASA) was added to 5% by weight relative to the reagents [15]; in the synthesis of the gels of HEC/PAAm previously described, ASA is added before the cross-linker.

2.4. Infrared Spectroscopy. For the qualitative identification of the functional groups of HEC/PAAM films, a Perkin-Elmer Fourier transform spectrometer model Spectrum One was used with the ATR accessory, with a frequency range of 4000-600 cm^{-1}.

2.5. Particle Size. A Tepper model TP1 spectrophotometer was used, with incident light at a wavelength of 670 nm for heating and 540 nm for cooling, the temperature range was 30 to 80°C, and for high concentrations of 5 at 95°C, the measurement speed was 10°C/min.

2.5.1. Analysis of Particle Size. This analysis was made using the PL-PSDA particle size distribution analyzer equipment from Polymer Laboratories with a series of quasi-monodisperse polystyrene latexes manufactured by Duke Scientific as calibration standards. A type I cartridge, with an operational range of 5 to 300 nm, was selected, and the effluent flow was 2 mL/min. Solutions containing 20 mg of sample in 20 mL of solvent were filtered through a Whatman filter of 2 μm before analysis, and the injection volume was 20 μL.

2.6. Differential Scanning Calorimetry (DSC). For this analysis, a PerkinElmer Pyris 1 differential scanning calorimeter was used, with a sample amount of 5 to 10 mg deposited in aluminum capsules, and a heating ramp of 10°C/min was used in a range of 25°C up to 200°C using a flow of nitrogen.

2.7. Mechanical Dynamic Analysis. The DMA analysis was made in a DMA equipment brand TA Instruments model 2980, in the multifrequency mode using a 35 mm long film tension-type clamp. The heating ramp was 5°C/min using a frequency of 1 Hz in a temperature range of 0 to 250°C.

2.8. SEM. The equipment used was a scanning electron microscope JEOL model JSM 6390LV; it was not necessary to modify with Au the surface of the samples since it was worked under low vacuum. This technique will be useful to observe the surface of the films and the incorporation of the drugs in them.

2.9. Atomic Force Microscopy (AFM). A Veeco di CP-II brand atomic force microscope with software Vr 5.01 was used. The analysis was done without cryo-fracture in non-contact tapping mode. The type of cantilever was rotated from monolithic silicone with a gold coating of 70 nm at a resonance frequency of 145-230 kHz.

2.10. Kinetics. The ultraviolet light spectrometer (Perkin Elmer model Lambda 10) was used for the calibration curves for the drug in ethanol-water and in buffer solution. With the data of the absorbances as a function of time, the release profiles (drug concentration released as a function of time) will be obtained, and the percentages of drug released from the gels will be calculated. In addition, the nature of the diffusion of the ASA drug in the HEC/PAAm gels will be determined to indicate which model is suitable. Among the most used mathematical models to analyze and describe the mechanism by which the liberation process occurs are those proposed by Higuchi in 1963 and Korsmeyer and Peppas in 1983 [16, 17].

Higuchi proposed a mathematical model used to describe the empirical drug release process, which complies with Fick's Law and is represented as follows:

$$\frac{M_t}{M_\infty} = K \cdot t^{1/2}, \quad (1)$$

where M_t/M_∞ is the fraction of drug released at time t and k is the release rate constant. On the other hand, Korsmeyer and Peppas proposed a mathematical model that is generally linear for values of $M_t/M_\infty < 0.6$. This model attempts to explain mechanisms of drug release where erosion and/or dissolution of the matrix occurs and is no more than a generalized form of the Higuchi equation that is expressed as:

$$\frac{M_t}{M_\infty} = K \cdot t^n, \quad (2)$$

where k is the release constant of the release system that incorporates structural and graphic factors of the drug release and release system.

The value of the exponent n provides information about the kinetics of drug release, so if n is equal to 0.5, the release of the drug takes place through a diffusion phenomenon of the Fickian type (mathematical model of Higuchi); if it does not take the values between 0.5 and 1, it indicates that the release of the drug is due to a non-Fickian or abnormal diffusion mechanism, and when it is equal to 1, the mechanism of drug release depends on the release process of the polymer chains [18]. To study the release of ASA from these polymer matrices, we proceeded with Equation (2). Matlab software 2016 was used to simulate the kinetic release.

3. Results

3.1. Infrared Spectroscopy. Figure 1 shows the spectrums for the HEC/PAAm gel and the gels with ASA incorporated by swelling and on the synthesis. The spectrum of HEC/-PAAm gel shows the corresponding peak stretches NH and OH to 3346 and 3186 cm^{-1}, respectively; the symmetrical and asymmetric stretches of CH_2 of the cellulose are located at 2921 and 2863 cm^{-1}, that of the stretching of the carbonyl group from PAAm is at 1672 cm^{-1}, that of the CN stretch of the polyacrylamide is seen at 1283 cm^{-1}, and finally that of the C-O-C stretch of HEC is located at 1088 cm^{-1}.

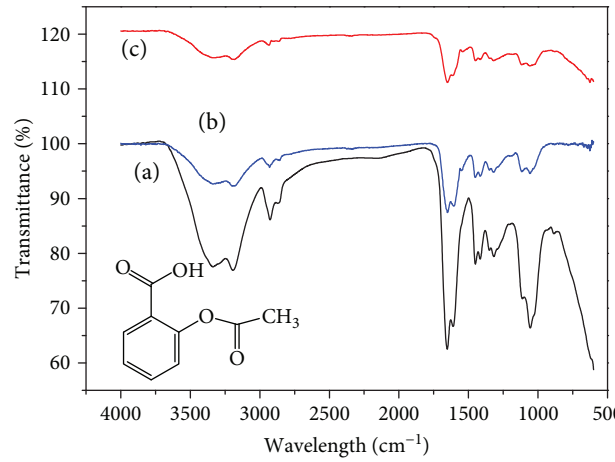

Figure 1: Infrared spectrum of (a) HEC/PAAm xerogel, (b) HEC/PAAm xerogel with ASA incorporated by swelling, and (c) HEC/PAAm xerogel with ASA incorporated on synthesis.

Bands belonging to the ASA drug are also observed: one of them coincides with that of the gel of OH at 3346 cm^{-1}, that of the asymmetric stretch C=O of the ester at 1754 cm^{-1}, a peak attributable to the C=O stretching of acid carboxyl at 1672 cm^{-1}, symmetric stretching for the acetoxy group at 1454, and symmetric stretching for the carboxyl group at 1411 cm^{-1}. The bands are located at 2921 and 2863 cm^{-1}, whose assignments correspond to the CH_3 and CH_2 groups that are part of both the polymer and the ASA molecule, thereby confirming the interaction between them. These results are similar to those reported by Nita [19] and Yang and Wang [20].

The IR spectrum of the HEC/PAAm sample with ASA incorporated on synthesis. In the same way as in the previous case, the functional groups of the gel is identified, as well as the main assignments of the drug; the vibration of OH at 3257 cm^{-1}, the asymmetric stretch C=O of the ester at 1676 cm^{-1}, and the stretch C=O of the carboxylic acid are not appreciated, perhaps because they moved to the right and are overlapped with the band of the carbonyl group of the gel. The peak of the symmetric stretch for the acetoxy group is located at 1454 cm^{-1}, and the symmetric stretch for the carboxyl group is at 1418 cm^{-1}.

3.2. Mechanical Dynamic Analysis (DMA). Figure 2 corresponds to the tan delta curved thermogram and the curved thermogram of the HEC/PAAm film storage module. In the curve tan delta against temperature, the secondary relaxations of the material between 50 and 75°C are observed, which are attributed to chain movements, rearrangements, or relaxations of an amorphous region; like the previous samples, there is a very pronounced peak that corresponds to T_g at 185° C.

Figure 3 shows the thermogram of the HEC/PAAm gel with ASA incorporated in synthesis; a transition that is attributed to T_g is identified around 115.3°C and then a peak at 117°C due to the active principle. It has been shown that the thermograms of the hydrogels with ASA do not coincide with those of the active principle nor with that of hydrogel

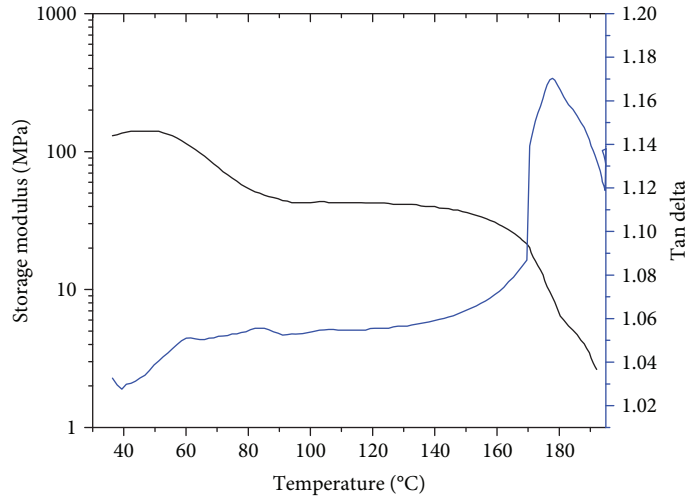

Figure 2: DMA from the xerogel HEC/PAAm.

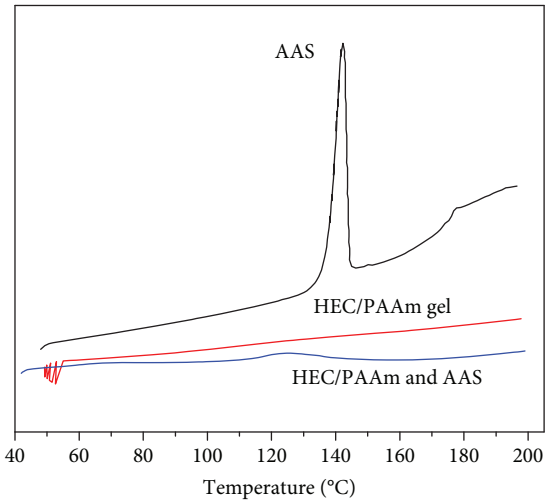

Figure 3: DSC-thermogram from the xerogel HEC/PAAm, ASA and HEC/PAAm and ASA.

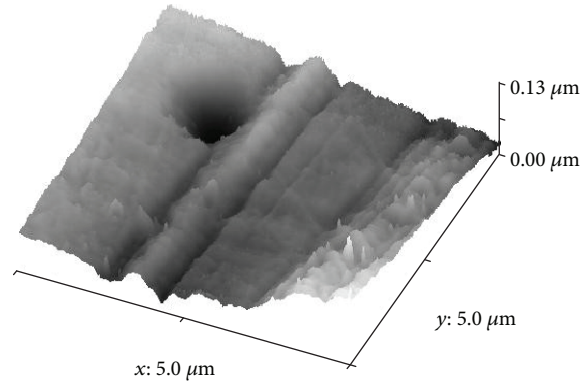

Figure 4: Atomic force micrograph of the HEC/PAAm xerogel.

alone. Therefore, we can say that a drug-polymer interaction occurs, which is an indication that the drug is inside the polymer matrix. This is consistent with that reported by Rodríguez-Llimos et al. [21].

3.3. Analysis of the Surface of the Gels. Figure 4 shows the atomic force micrograph of the HEC/PAAm xerogel; like the SEM photographs in AFM micrographs, the surface is a little warped and has some micelles on the surface that measure 0.05 to 0.1 μm. The micrograph shows a hole in the surface; the wrinkling of the surface is due to the shrinkage of the samples during drying, which is similar to what has been observed in other works, where the differences in the drying process lead to different types of pores and "wrinkles" on the surface of HEC gels. Pore sizes between 13 microns were found, similar to those obtained by Petrov et al., which reported between 20 and 200 microns in pore size, and the corrugated walls are approximately 0.25 microns [22, 23].

The surface morphology of HEC/PAAm xerogels is at 100x (Figure 5(a)). The xerogels show a uniform, smooth, homogeneous surface. In most of the film, crater-like reliefs are also observed after doing the washings and letting the film dry again; this type of behavior was observed when drying the gels of HEC either by a conventional method or by cryogenic HEC, which tends to form undulations as observed by Petrov et al. [22, 23]. The incorporation of ASA in HEC/PAAm xerogels by swelling is shown in Figure 5(b), where the morphology surface clearly shows the formation of irregular orthorhombic white crystals, from 4 to 10 μm long of the drug distributed on the surface of the film, which in turn has a homogeneous morphology with certain parts more pronounced as waves. The shade of the crystals is more transparent and opaque.

The HEC/PAAm xerogel with ASA incorporated in synthesis (5c); in the images, a homogeneous, smooth surface like the one that corresponds to the gel without the drug is seen in the background. In relief, the agglomeration of white particles is observed and in others the accumulation of particles in the form of arborescent branches; the shape of these structures had not been appreciated in the films with drug incorporated by swelling, so they are attributed to the way in which the

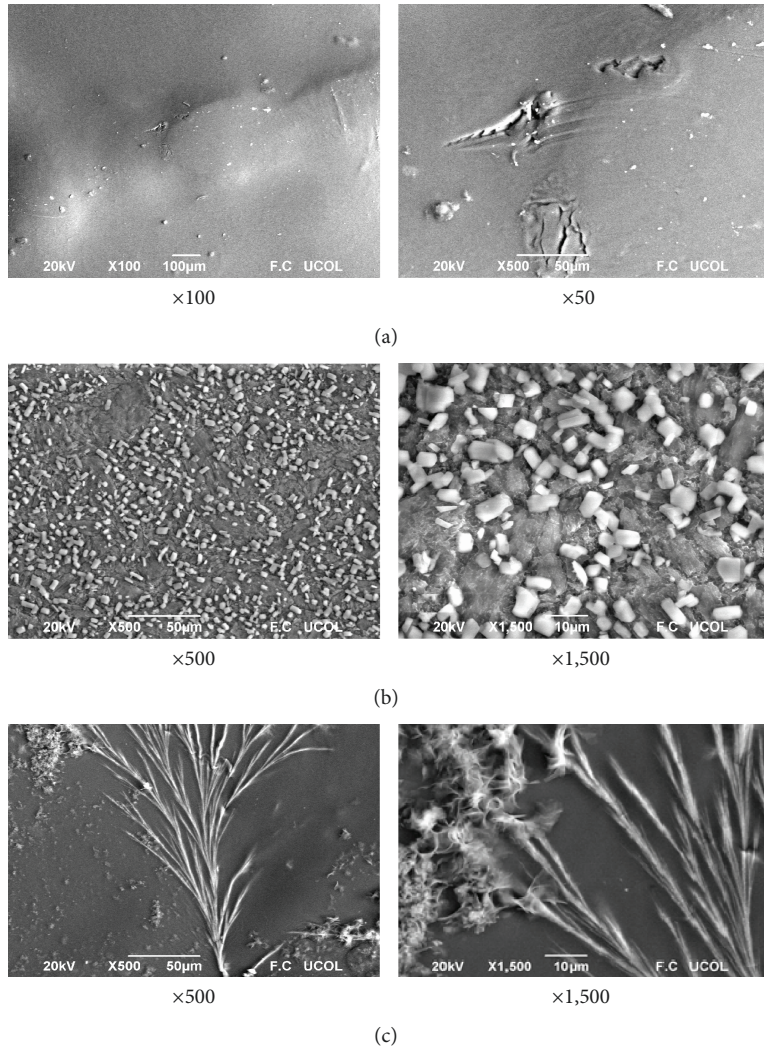

Figure 5: Micrographs with magnifications, the samples are (a) xerogel of HEC/PAAm without drug, (b) xerogel of HEC/PAAm with drug ASA incorporated by swelling, and (c) xerogel of HEC/PAAm with drug ASA incorporated in the synthesis.

incorporation of the drug was made, to all the conditions since it was in contact with reagents during the synthesis.

3.3.1. X-Rays. In Figure 6, the "X"-rays of xerogels with incorporated ASA are shown, either by swelling or by synthesis. Pure acetylsalicylic acid has definite peaks in the X-ray patterns, where the crystal size is 54 nm calculated with the Debye-Scherrer equation [24]. In the case of xerogels, the xerogels of HEC/PAAm, a broad peak ranging from 15 to 40° is completely amorphous. It is known that the growth of the crystals depends on the solvent, temperature, and pressure [25], and there is some confusion in the sizes of the crystals or the indexation. In the case of the gels, where ASA was incorporated by swelling, there is an increase in the height of the peak, compared to the xerogel with the ASA incorporated by synthesis.

3.3.2. Drug Release. Below the UCST and above the LCST, the polymer was insoluble in water and the solution was physically cloudy and whitish. Above the UCST and below the LCST, the polymer was soluble in water and the solution was clear, forming then a small "window of solubility"

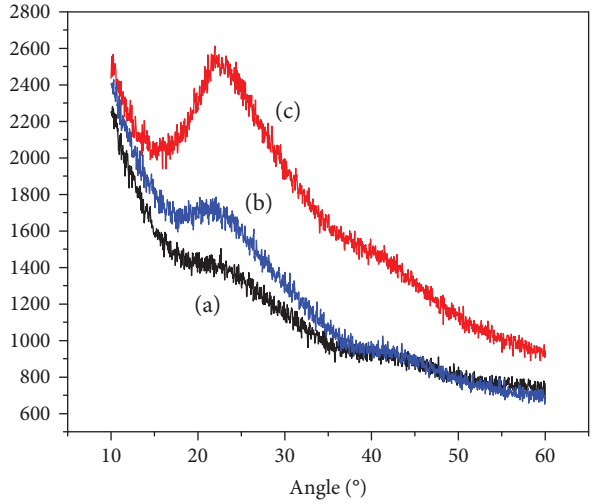

Figure 6: X-rays of HEC/PAAm xerogel (a) and HEC/PAAm xerogel with ASA incorporated by synthesis (b) and by swelling (c).

[26]; these phenomena are associated with the functional groups of the polymer-solvent system, the entropy change, and the solvent-polymer interaction parameter [26–28]. The LCST is attributed to the change in the dipole moment of the molecule by increasing the temperature of the polymer. The UCST temperature is attributed to the decrease in the entropy of the system that occurs when the solution is cooled. It should be remembered that for a polymer to dissolve in a solvent, the functional groups of both must be similar and the entropy must increase [29]. The HEC/PAAm gel has an LCST of 41°C, which indicates that below this temperature the release of the drug will be presented; this temperature and a particle size between 124 and 167 microns were determined by turbidimetry. These values are between normal for cellulose derivatives such as hydroxypropyl cellulose/PAAM as reported by Castro et al..

Figures 7 and 8 show the release of ASA from HEC/PAAm hydrogels at three temperatures in buffer solution and ethanol-water, respectively. In both graphs, it is observed that around 120 minutes the release is done more quickly and then more slowly until a maximum concentration is obtained around 480 minutes. The release of ASA is constant from the first hour, releasing 0.3 mg/hr·m. The simulation was done in Matlab.

The results obtained from the release in buffer (Figure 7) are also consistent with the relationship between the released concentration and the temperature as reported in bibliographic sources since the lowest concentration was at 37°C with 0.1657 mg/mL and the highest at 39°C with 0.3144 mg/mL. In regard to ethanol-water release data (Figure 8) for the same type of gel, it can be seen that as the temperature increases, the concentrations of drug released tend to decrease. On the other hand, it is observed that the HEC/PAAm gel at 35°C in ethanol-water released more amount of ASA (0.3941 mg/mL).

With the results obtained from the drug releases made in the two types of films and using the different solvents, the kinetic study was performed using the mathematical model represented in Equation 2.3, proposed by Higuchi in 1963 and Korsmeyer and Peppas in 1983, where M_t/M_∞ represents the fraction of drug released, k is a constant of proportionality, and n is the mode of transport of the drug [30]. To know if the mechanism of drug release is of Fickian or anomalous type, the mode of transport n should be calculated. Where n has a value of 0.5, the release of the drug follows the Fickian diffusion mechanism; if n is different from 0.5, the diffusion mechanism is considered non-Fickian or anomalous, and when n is equal to 1, it is considered to follow the Schott diffusion mechanism [31, 32].

Table 1 shows the values of n obtained for the release of ASA from the hydrogels in the xerogel state both incorporated by swelling and in the synthesis and in both solvents used, at three temperatures. Unfortunately, the results of the kinetics of ASA are very irregular, and the values of n are less than 0.5, so they do not correspond to any of the intervals described by Katime (2004), which indicates the existence of several simultaneous processes to the phenomenon of dissemination of ASA. These results are consistent with those reported by Aragón et al. [33].

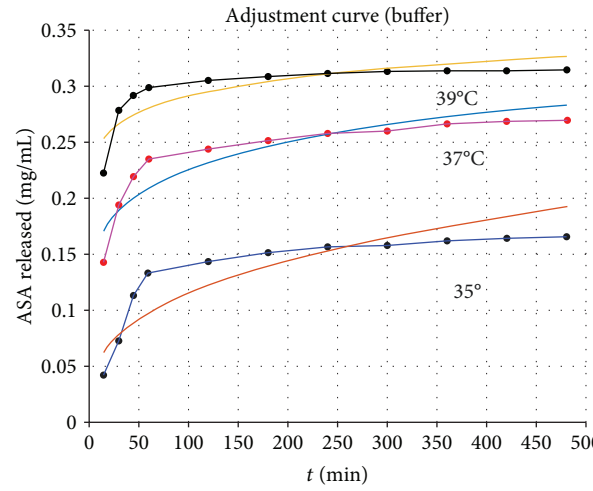

Figure 7: Adjustment curve for ASA released with buffer solution experimental data using Matlab.

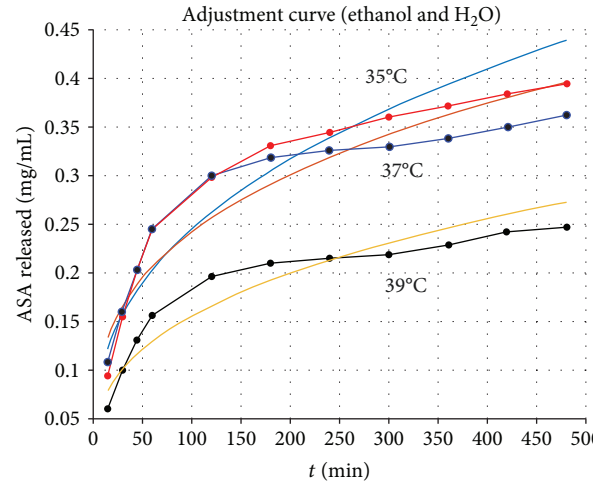

Figure 8: Adjustment curve for ASA released with ethanol-water solution experimental data using Matlab.

The adjustment of the experimental data was made using the Higuchi model, using the Matlab software version 2016, (Supplementary Materials (available here), which the program used). For the two solutions of ethanol-water and buffer for the temperatures of 35, 37, and 39°C, it is observed that as one for each temperature, in the case of buffer solution the curves were better adjusted to the data, while in regard to ethanol water solution no adjustment to the data is observed.

On the other hand, we have ANOVA for the data as shown in Table 2, in the two solutions with the temperatures of 35, 37, and 39°C. The error calculated for the simulated data and with the Matlab software has a greater error in the first-order model, three decimal places in a range 0.0042-0.0084, and for the Higuchi model error of eleven decimal places in a range of $9.169E-11$ to $6.52E-11$.

The R^2 confidence level for the first-order model of 0.442-0.790 or below 80% for both solvents indicates that it is

Table 1: Values of n calculated for the kinetics of ASA release from xerogels.

Hydrogel	Method of incorporation	Solvent of release	35 C		37°C		39°C	
			n	k	n	k	n	k
HEC/PAAm	Swelling	Buffer	0.1485	0.4353	0.3249	0.1558	0.0733	0.6594
HEC/PAAm	Swelling	E_A	0.3701	0.113	0.3131	0.1582	0.3576	0.1218

Table 2: ANOVA data from the "first-order" equation and Higuchi model simulation.

Solvent	Temperature (°C)	First order			Higuchi model data		
		Error	R^2	F^0	Error	R^2	F^0
Buffer	35	0.0044	0.432	$8.4101E-06$	$6.6615E^{-11}$	0.902	$8.41005E-06$
Buffer	37	0.0059	0.581	$1.2142E-06$	$7.5046E^{-11}$	0.941	$1.21422E-06$
Buffer	39	0.0042	0.442	$1.6866E-05$	$9.1696E^{-11}$	0.882	$1.68663E-05$
Ethanol-water	35	0.0084	0.790	$3.887E-07$	$6.8622E^{-11}$	0.949	$6.7894E-07$
Ethanol-water	37	0.0080	0.734	$9.1803E-07$	$7.5030E^{-11}$	0.939	$1.40442E-06$
Ethanol-water	39	0.0057	0.442	$4.7177E-07$	$6.5236E^{-11}$	0.947	$8.01275E-07$

not the "first order," while for the Higuchi model the value of R^2 is in the range of 0.882-0.947 or, in other words, above 90% for both solutions, which indicates that the release of ASA is done by this model. Another important value to measure is that F^0 is not statistically significant for the "first order" for both solvents and at all temperatures; contrary to this, the Higuchi model suggests that it is statistically significant.

The controlled release of ASA is 0.35 mg/hour, which is enough for the application of a dermatological compress to control or eliminate acne. At the beginning of the dermatological infection, the temperature rises and becomes red, with a temperature up to 39°C, where a greater amount of ASA will be released; later, the skin will lower the temperature due to the action of the drug, which will mean that less amount of drug is needed, to ensure that the amount of this drug is slow to avoid a possible allergy to the drug.

The active release of the drug is possible on the skin due to the biomacromolecules present in the skin, due to temperature, pH, stimulation, etc. This release of the drug is active due to the diffusion of ASA contained in the drug matrix towards the epidermis of the skin (Figure 9). It is expected to prove with primary bioessays to conclude the work in a next investigation.

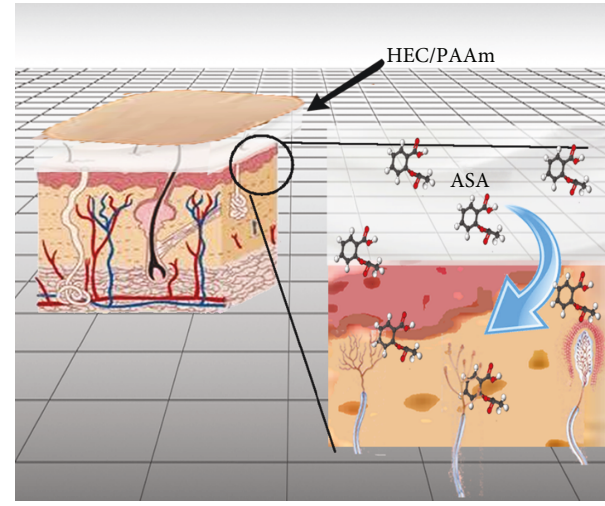

Figure 9: Schematic representation of ASA of the hydrogel entering the dermis.

4. Conclusions

The incorporation of ASA in the HEC/PAAm gels was possible by means of swelling, without modifying the drug in the incorporation. On the other hand, in the incorporation of ASA in the synthesis of the HEC/PAAm gel, the drug is in smaller quantity; in SEM microscopy, it is observed that ASA tends to form arborecencias and not form defined crystals, together with the appearance of the gel which changed the color yellow.

The spectrum of FTIR has the characteristic bands of the drug ASA, 2921 and 2863 cm^{-1}, whose assignments correspond to the CH_3 and CH_2 groups that are part of both the polymer and the ASA molecule. The DSC showed that the drug is present in the gel at 115°C; in the DMA, it is shown that the HEC/PAAm gel has chain movement. The drug release is carried out according to the "Higuchi" model, in ethanol-water and buffer solutions, and it is simulated; the ANOVA of the data informs us that it has a confidence level of 90%. In the application of this drug in a dermatological pad for the control or elimination of acne, at the beginning this has redness and a temperature rise, taking that at 39, 37, and 35°C the release at a higher temperature is constant with time.

Data Availability

The simulation data used to support the findings of this study are included within the supplementary information file.

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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Supplementary Materials

Simulation in Matlab to obtain the adjustment curve, error, and coefficients of the experimental data from the ASA released in solution ethanol water and buffer. *(Supplementary Materials)*

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