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# Synthesis and Application of Poly(ethylene-*co*-vinylalcohol-*graft*-acetylsalicylic acid) in Drug Delivery Domain

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**ABSTRACT:** A series of poly(vinylalcohol-*co*-ethylene-*graft*-acetylsalicylic acid) hydrogel ($H_i$) of different acetylsalicylic acid (AcSa) contents were prepared by grafting of AcSa groups to poly(vinylalcohol-*co*-ethylene) in an esterification reaction and then crosslinking with oxalic acid. The $H_i$ was characterized by the solubility test, DSC, NMR, and SEM analyses. The AcSa released by retroesterification of $H_i$ at 37°C and at different pHs during 92 h. The results revealed that the amount of AcSa released from $H_i$ depended on the initial content of AcSa in $H_i$ and the pH of the media. In general, the results revealed that the PEVA-*graft*-AcSa ($H_2$), which contained initially 1.59 mg of AcSa, released at pH 1 a lower amount of AcSa (0.08 ± 0.02 wt % of AcSa/h), stable during the longest period (85 h). On the reverse $H_3$ which contained 2.05 mg of AcSa presented a highly efficient release rate at pH 7. This hydrogel was able to release 0.80 ± 0.05 wt % of AcSa/h, stable for about 60 h. From the first view, this finding seemed to be very important in the drug-release domain, because the hydrogel prepared in this work was able to release a greatest amount of aspirin directly into the intestines (neutral pH). © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

**KEYWORDS:** poly(vinylalcohol-*co*-ethylene-*graft*-acetylsalicylic acid); acetylsalicylic acid; release; retroesterification

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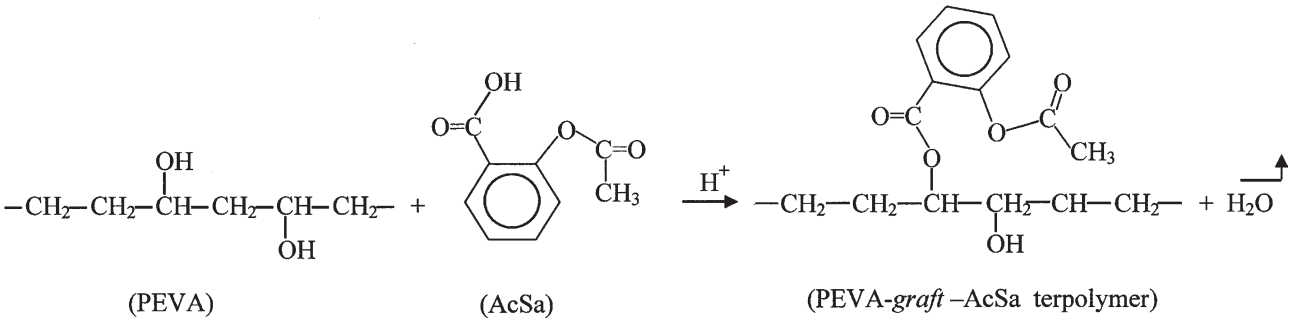
## INTRODUCTION

The use of biocompatible and biodegradable polymers, have received a considerable attention in the last decade. Thermoresponsive hydrogels have recently become more attractive in the biomedical domain; its use included controlled drug delivery which the crosslinked poly(vinylacohol) (PVA) is a typical one. This hydrogel swells in water or aqueous solution below the lower critical solution temperature (LCST) and shrinks above LCST.[1–6] This polymer is often used in drug delivery and medicine. Varshosaz et al.[7] have studied the concentration of the cross-linking agent (glutaraldehyde) in PVA films and the percentage of the theophylline (drug) in the hydrogels. It was found that the drug-release rate and diffusion coefficient increased with PVA content in the hydrogel and also with the amount of the loaded drug. While glutaraldehyde had a reverse effect, the pH did not affect the swelling and diffusion coefficient. Pal et al.[8] have developed poly(vinyalcohol–gelatin) patches to be used as polymer matrix, where salicylic acid was incorporated. The release of the drug from the patches followed Higuchan/Fickian kinetics, indicating a diffusion-controlled release process. Orienti et al.[9] have crosslinked PVA with ethylene glycoldiglycidylether to obtain hydrogel-forming polymers. The polymers were also substituted with oleoyl chloride, providing hydrogels with weak solubility. The results obtained indicated that the crosslinked polymers slow down the release of the drugs with respect to the pure drug at each pH. The degree of crosslinking of ethylene glycoldiglycidylether and the extent of the substitution with oleoyl chloride were found to influence drug release.

Poly(vinylalcohol-*co*-ethylene) (PEVA) is practically unknown in the drug-release domain. Only some works were investigated in this field.[10] PEVA is a copolymer biodegradable and widely used in food packaging because of its nontoxicity. Such copolymer which contained a low ethylene unit is susceptible to be degraded and by this way continue the complete biodegradation of the material notably in the presence of enzymes.[11–14] The presence of ethylene units in PEVA hydrogel reduces its high swelling degree and by this way allows this material with no doubt to have a good performance in drug delivery field. PEVA was used as a support for drug delivery by Young et al.[10] and doxorubicin was used as a model drug. It was found that doxorubicin in this copolymer matrix showed a two-step release behavior. The drug release in the first step was rapid. This observation was attributed to the macroscopic pores that drug distributing outside the particles diffused through rapidly. On the other hand, the drug release in the second step was slow and prolonged.




**Scheme 1.** Preparation of PEVA-*graft*-AcSa terpolymer by esterification reaction.

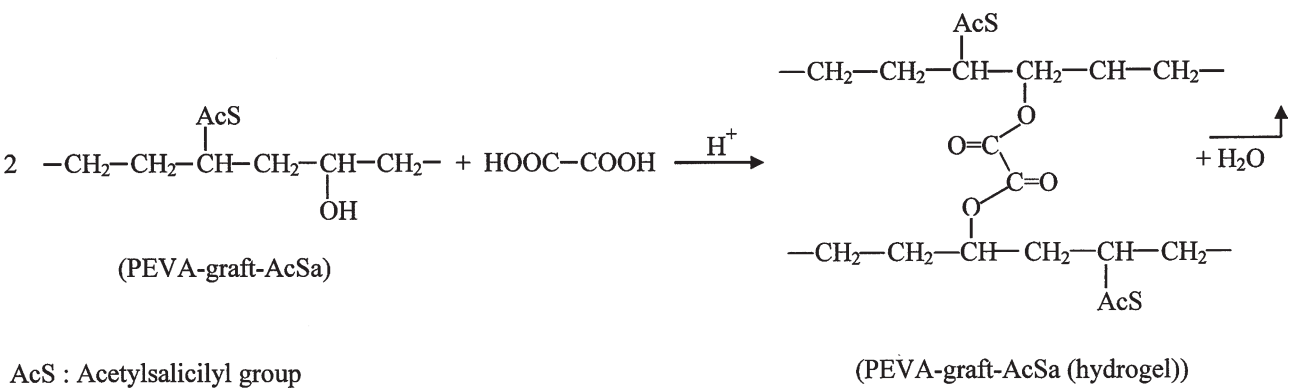
Acetylsalicylic acid called aspirin is a part of a group of medication called nonsteroidal anti-inflammatory drugs (NSAIDs). It prolongs bleeding time and inhibits platelet aggregation. Aspirin is widely used for the relief of pain.[15,16] Today, it is one of the most widely used medications in the world, with an estimated 40.000 tones of it being consumed each year.[17] Aspirin has a direct irritant effect on gastric mucosa due to an inhibition of prostaglandins, prostacyclins, thus causes ulceration, epigastric distress, and/or hemorrhage.[18] Sustained release of aspirin formulation would reduce the undesired side effects, reduce frequency of administration, and improve patient compliance.[19] Several investigations have been developed to obtain a system of drugs delivery in which encapsulation or microencapsulation techniques have been used extensively,[20–26] where solvent evaporation was used with different polymeric matrix and different experimental conditions. Several polymers are sensitive to pH changes. These polymeric materials have the characteristic of protecting the drug from the action of enzymes and gastric fluids, which are in fact very acidic.[27–31] Junquin et al.[32] have studied the factors influencing the release of salicylic acid from poly(methacrylate-*co*-amino-ester) films using the differential scanning calorimetry method. This technique was performed on the polymeric films to study the solubility of the drug in the polymer. The results obtained were an increase in both of drug dry rate released with increasing temperature and adsorption of salicylic acid by the polymer. This finding was believed to influence the drug-release profiles observed for different drug loadings, ionic strengths, and the drug–polymer because of the interactions that occurred. Gavhane et al.[33] have investigated the effect of pH of microenvironment within the polymer matrix on drug release and studied the interference of polymer and drug solubility. It was found that as the pH of microenvironment increased, the rate of the drug release increased in a linear relationship. Zhuang et al.[34] have used poly(*N*-isopropylacrylamide-*co*-*N*-vinylpyrrolidone) and poly(*N*-isopropylacrylamide)/poly(*N*-vinylpyrrolidone) interpenetrating polymer network (INP) synthesized by radiation polymerization. Acetylsalicylic acid was used as a model drug in this investigation. It was observed from the results obtained that these materials had a higher drug release in a physiological environment and showed that these hydrogels were promising materials for causing solubilization and developing a long-term controlled release system.

In this present work, a series of crosslinked poly(vinylalcohol-*co*-ethylene-*graft*-acetylsalicylic acid) containing different acetylsalicylic (AcSa) contents were synthesized by grafting of AcSa on PEVA using an esterification reaction. The release process of acetylsalicylic acid from hydrogels formed occurred by retroesterification reaction at 37°C following a duration of 92 h in media of pH 1, 3, 5, and 7. The kinetic of AcSa released and the effect of the initial AcSa content were studied.

## EXPERIMENTAL

### Materials

Poly(vinylalcohol-*co*-ethylene) (PEVA) purchased from Aldrich contained 27 mol % of ethylene units with an average molecular weight number of 29,000 g/mol. Acetylsalicylic acid (AcSa) (98 wt % purity) (Aldrich) was used without purification.




**Scheme 2.** The crosslinking reaction of poly(vinylalcohol-*co*-ethylene).

**Table I.** Preparation Conditions of PEVA-*graft*-AcSa Hydrogels ($H_i$)

| PEVA-*graft*-AcSA | PEVA (g) | AcSa (g) | Oxalic acid (g) | DMF (mL) |
|---|---|---|---|---|
| $H_1$ | 1.500 | 0.50 | 0.016 | 7.0 |
| $H_2$ | 1.500 | 0.57 | 0.016 | 7.0 |
| $H_3$ | 1.500 | 0.75 | 0.016 | 7.0 |
| $H_4$ | 1.500 | 0.92 | 0.015 | 7.0 |
| $H_5$ | 1.500 | 1.89 | 0.014 | 7.0 |

Dimethylformamide (DMF) (98 wt % purity) (Aldrich) was used in this work as a solvent.

### Preparation of PEVA-*graft*-AcSA Hydrogel

PEVA solution was prepared in a concentration of 10 wt % by dissolving dried pellets of PEVA in DMF at 90°C with continuous stirring during 24 h. PEVA/AcSa mixtures were prepared by mixing different loading percentages of AcSa in calculated amounts of PEVA. PEVA-*graft*- AcSa terpolymers were obtained by esterification reaction of PEVA with AcSa in DMF, acidified with three or four drops of concentrated sulfuric acid and heated at 60°C for 72 h according to the reaction (Scheme 1).

PEVA-*graft*-AcSa terpolymers obtained were completely soluble in DMF. To increase the yield in PEVA-*graft*-AcSa terpolymer, the water produced during the esterification reaction has been removed by evaporation under reduced pressure. The PEVA-*graft*-AcSa hydrogel films ($H_i$) were prepared by adding small amounts of oxalic acid to the solutions of PEVA-*graft*-AcSa terpolymer in DMF (Scheme 2), and then the solution was casted by slow evaporation at room temperature for 1 week and heated at 90°C for 24 h under vacuum. The preparation conditions of PEVA-*graft*-AcSa hydrogels films ($H_i$) are gathered in Table I.

### Characterization

The total, grafted, and free acetylsalicylic acid contained in PEVA-*graft*-AcSa hydrogels samples were determined quantitatively in DMF by $^{13}$C-NMR spectroscopy at 200 MHz in DMF before the crosslinking operation using JEOL FX 90 Q-NMR apparatus. The determination of the total amount of AcSa by $^{13}$C-NMR was based on the quantitative comparison of aromatic carbons area of acetylsalicylate units localized between 128.5 and 133.5 ppm and those of C in α-position of the vinyl alcohol units. On the other hand, the free AcSa content was calculated from the quantitative comparison of the area localized between 168.0 and 174.2 ppm assigned to the carbon of the carboxylic groups and those of the aromatic groups determined previously. The AcSa grafted was calculated from the difference between the total and the free amount of AcSa. The amounts of AcSa grafted were confirmed by UV–visible spectroscopy using Aultropec 2100 pro, Amersham Biosciences spectroscope. PEVA-*graft*-AcSa was purified from the residual acetylsalicylic acid by dissolution in DMF and precipitation in acetone. The analyses were realized at 276 nm in DMF from an acetylsalicylic acid calibration curve. The results obtained by the two methods are gathered in Table II. Acetylsalicylic acid released in water at different pHs from PEVA-*graft*-AcSa hydrogel films was also determined quantitatively by a UV–visible spectrometer at the same wavelength number.

**Table II.** Amounts of AcSa Free and Grafted in 4.5 mg of PEVA-*graft*-AcSa Terpolymers Determined by $^{13}$C-NMR and UV–Visible

| PEVA-*graft*-AcSA | Total AcSa (mg) | Free AcSa (residual) (mg) | AcSa grafted (mg) | |
|---|---|---|---|---|
| | | | $^{13}$C-NMR | UV-visible |
| $H_1$ | 1.95 | 0.36 | 1.59 | 1.64 |
| $H_2$ | 2.64 | 0.59 | 2.05 | 2.13 |
| $H_3$ | 1.62 | 0.35 | 1.27 | 1.34 |
| $H_4$ | 1.73 | 0.35 | 1.38 | 1.43 |
| $H_5$ | 1.38 | 0.29 | 1.09 | 1.14 |

The glass transition temperatures ($T_g$) of PEVA, AcSa-*graft*-PEVA hydrogel films were measured with DSC (Shimadsu DSC 60), previously calibrated with indium. Samples weighing between 10 and 12 mg were packed in aluminum DSC pans before placing in DSC cell. The samples were heated from 20 to 200°C at a heating rate of 20°C min$^{-1}$.

Scanning electron microscopic (SEM) graphs of dried thin films were obtained using Hitachi S4700 Field emission (Japan) for morphology analysis. Samples were coated with gold.

### In Vitro Drug-Release Studies

PEVA-*graft*-AcSa hydrogel films were suspended in 100 mL of water/hydrochloric acid solution at a fixed pH and stirred at 100 rpm at 37°C (body temperature). This experimentation occurred at pH 1, 3, 5, and 7. Aliquots of 0.5 mL were withdrawn at time intervals and immediately returned to the media just after analysis. This operation kept a constant volume of media during the release process. The total mass of AcSa

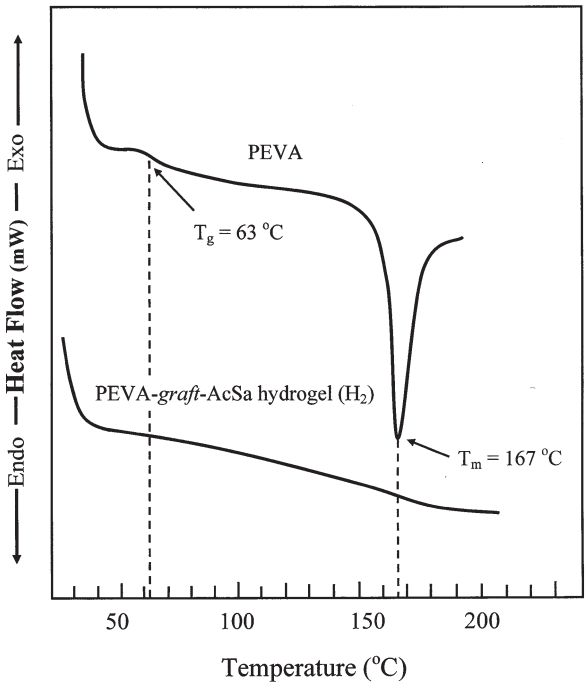



**Figure 1.** DSC thermograms of pure PEVA and PEVA-*graft*-AcSa hydrogel ($H_3$) obtained at heating rate of 20°C/min.

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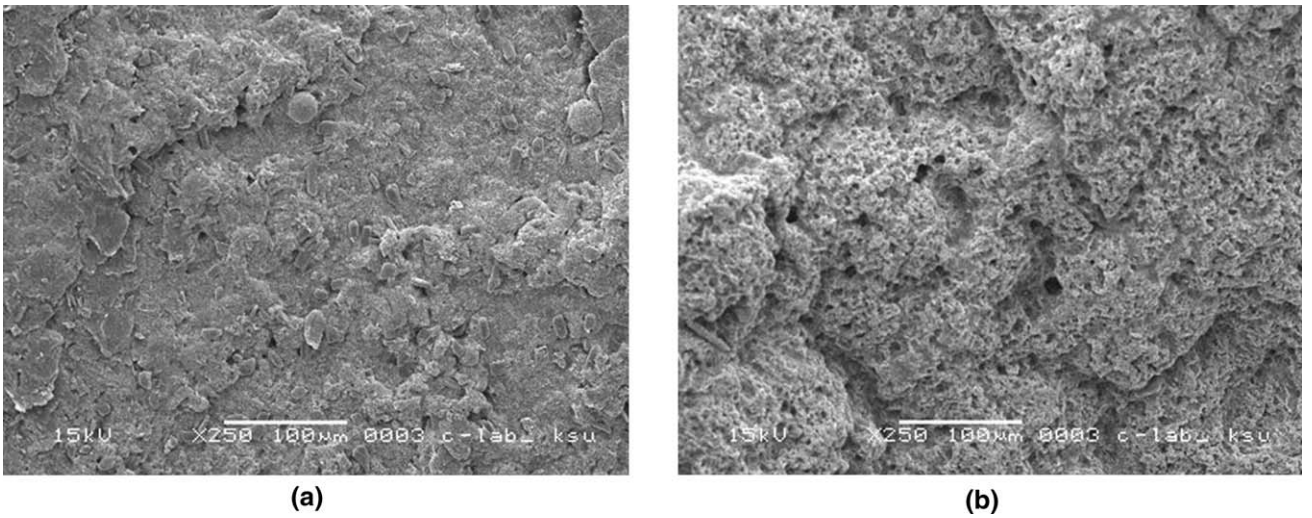


**Figure 2.** SEM micrograph of PEVA-*graft*-AcSa hydrogel ($H_2$): a) before the release process, b) after the release process.

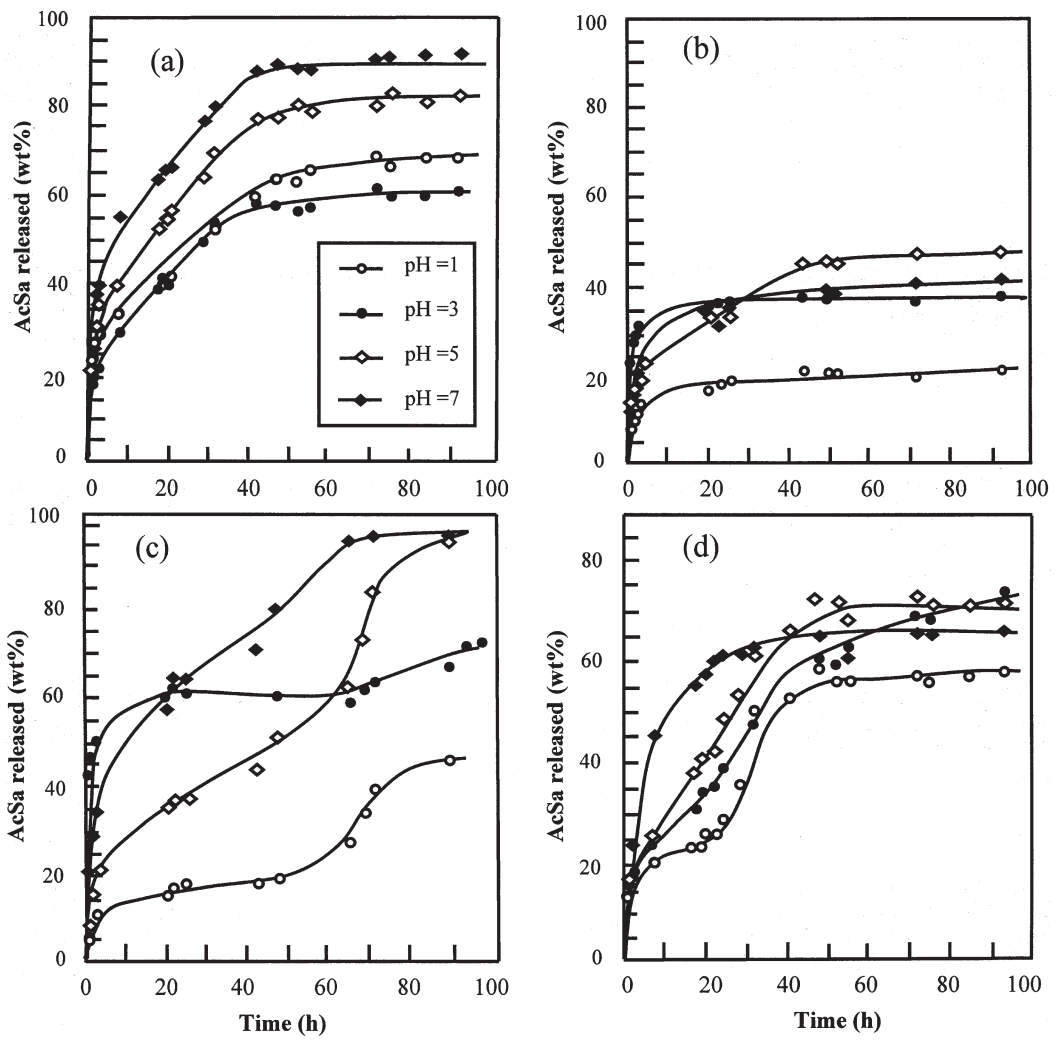


**Figure 3.** Acetylsalicylic acid (wt %) released from PEVA-*graft*-AcSa hydrogels versus the time at different pH. (a) $H_1$; (b) $H_2$; (c) $H_3$; (d) $H_4$.

released during a certain duration was calculated from the absorbance determined as mentioned above. It is important to note that during the release process the pH of water was practically not affected by the small amount of AcSa released, because the amount of AcSa released was negligible compared with those of media and acetylsalicylic acid has a low p$K_a$ value (3.5), therefore the addition of a buffer solution to water was not necessary.

## RESULTS AND DISCUSSION

### Characterization of PEVA-*graft*-AcSa Terpolymer

The process of obtaining a crosslinked PEVA-*graft*-AcSa ($H_i$) was proved easily by the insolubility test of this material in DMF and confirmed by DSC analysis. Indeed, the DSC thermogram of hydrogel showed in Figure 1 the total disappearance of the glass transition temperature ($T_g$) at 63°C and the melting temperature ($T_m$) at 167°C attributed to the pure PEVA. The amounts of AcSa amounts in PEVA-*graft*-AcSa terpolymers determined by UV are lightly overestimated due to the error of the dilution. On the SEM images of Figure 2 obtained for PEVA-*graft*-AcSa (hydrogel) film ($H_2$) before (Figure 2a) and after (Figure 2b) the release process, it was possible to see the differences in their morphology. The micrograph of $H_2$ taken as an example before the release process (Figure 2a) showed clearly the free AcSa encapsulated in the form of rectangular grains (7 $\mu$m × 12 $\mu$m). After 48 h of the release process, the same sample showed through the micrograph of Figure 2b a total disappearance of the microcapsules leaving the typical cavities and pores occupied initially by the free AcSa and the grafted AcSa, respectively.

### In Vitro Acetylsalicylic Acid Released Study

The acetylsalicylic acid released from PEVA-*graft*-AcSa hydrogel films occurred at 37°C (body temperature) according to the retroesterification reaction of scheme (2). Figures 3 and 4 show the release profiles of AcSa released at different pH from $H_1$, $H_2$, $H_3$, $H_4$, and $H_5$ during 92 h, respectively. According to these data, it was observed that the maximum amount of AcSa released was reached at pH 7 during about 60 h with $H_1$ (90 ± 3 wt %), $H_3$ (96 ± 2 wt %), and $H_5$ (95 ± 2 wt %) which contained initially 1.59, 1.27, and 1.09 mg of AcSa grafted, respectively. On the other hand, as shown in Figure 3b, the minimum amount of AcSa was obtained with $H_2$ (22 ± 2 wt %) at pH 1 during the same period. In the last case, the decrease of AcSa amount released could be attributed to the reduction of the hydrophilicity of $H_2$ in water, because this hydrogel contained a relatively higher ester grafted (2.05 mg). At this AcSa content, the hydrogel began to shrink; PEVA-*graft*-AcSa film was in a contracted state and swelled slowly. The amount of AcSa released was practically uniform during 80 h. The profiles of $H_3$ (1.27 mg) at different pHs (Figure 3c) and $H_4$ (1.38 mg) at pH 1 (Figure 3d) showed an irregularity (inflexion) indicating that the release process passed through two steps separated by a transition zone. The first one characterized by a quick increase of AcSa amount during the first 3–5 h, seemed to be due to the free AcSa (0.35 mg) released during this period. While the second one characterized by a slow increase of AcSa was localized in $H_3$ during a period localized between 60 and 70 h, and $H_4$ between 30 and 60 h indicating the release of the grafted AcSa. The same irregularity in the drug-release profile was also observed by Taranti et al.[35] using the poly(lactic acid)/drugs composites.

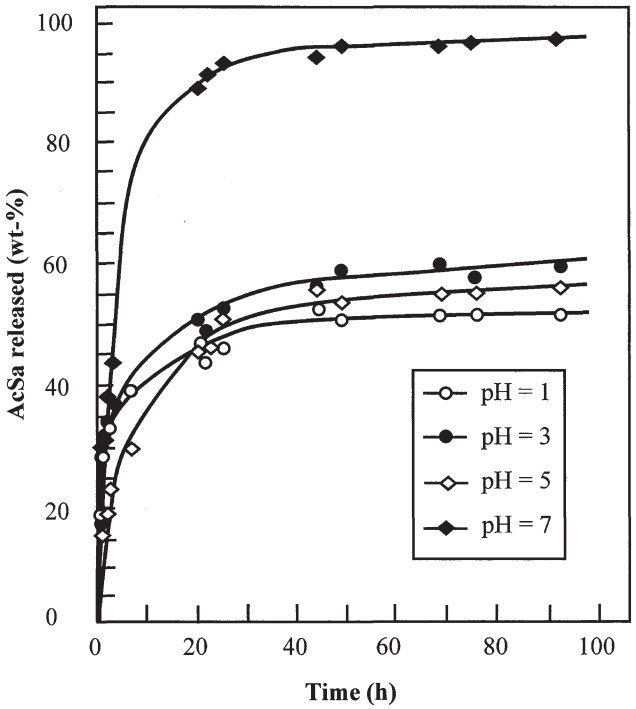


**Figure 4.** Acetylsalicylic acid (wt %) released from PEVA-*graft*-AcSa hydrogel ($H_5$) versus the time at different pH.

### Stability Study of the Instantaneous Release Rate of AcSa

Figures 5 and 6 show stable zones of AcSa-release rate at 37°C and different pHs for $H_1$, $H_2$, $H_3$, $H_4$, and $H_5$ versus time, respectively. On the light of Figure 5 profiles, $H_1$, $H_2$, $H_3$, and $H_4$ presented two important stable zones of release rate, while $H_5$ showed through Figure 6 only one stable zone. $H_1$ revealed that at all pH range the dynamic of AcSa released was divided in two important zones. The first one of the higher AcSa amount release rate was localized between 0.60 and 1.31 ± 0.03 wt %/h, stable during 35 h and the second was medium, localized between 0.06 and 0.08 ± 0.2 wt %/h during the last 45 h. Before the first 7 h in which the dynamic of AcSa released was very active, Figure 6 showed that, in all pHs, $H_5$ followed a weak release rate because during 55 h this material was able to release only an important rate localized between 0.04 and 0.08 ± 0.02 wt % of AcSa/h.

As showed in Figure 5c, except during the first 8 h of the release process, the maximum of AcSa amount released was reached in $H_3$ at pH 7. Indeed, such hydrogel was able to release 0.80 ± 0.5 wt % of AcSa/h stable during 60 h. When the pH of the media was equal to the unity, the same hydrogel was also able to release a minimum of 0.31 ± 0.02 wt % of AcSa/h stable during about 53 h.

In general, these results also revealed in Figure 5b that the PEVA-*graft*-AcSa ($H_2$) released at pH 1 a lower amount of AcSa

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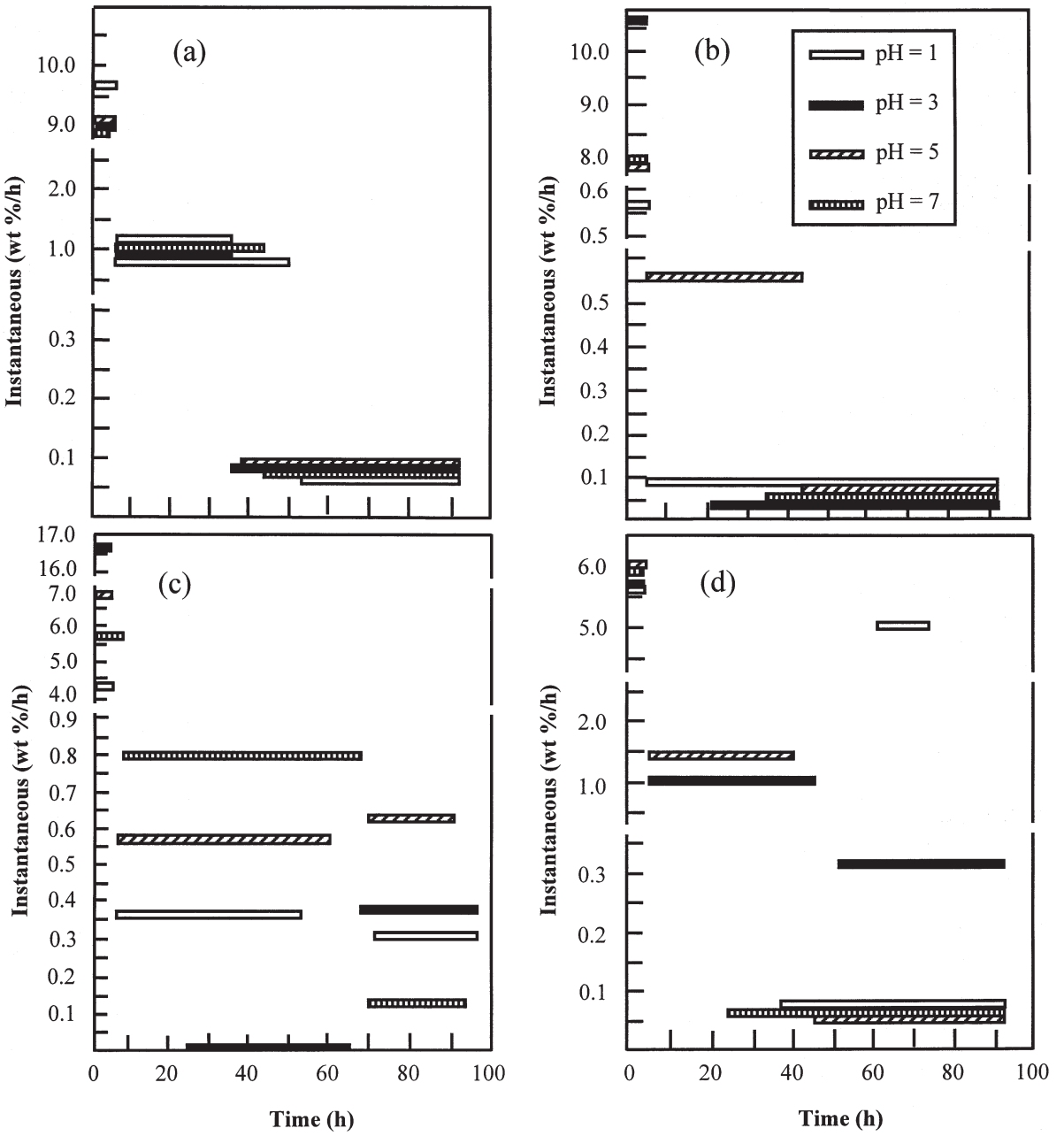


**Figure 5.** Stability zone of instantaneous rate of AcSa released from AcSa-*graft*-PEVA hydrogels ($H_1$, $H_2$, $H_3$, $H_4$) versus the time at 37°C. (a) $H_1$; (b) $H_2$; (c) $H_3$; (d) $H_4$.

(0.08 ± 0.02 wt % of AcSa/h) stable during the longest period (85 h). On the reverse, $H_3$ presented as showed in Figure 5c a highly efficient release at pH 7. From the first view, this finding seemed to be very important in drug-release domain, because $H_3$ was able to release the greatest amount of Aspirin directly into the intestines (neutral pH) and not in the stomach (pH 1).

### Effect of the Initial Amount AcSa Grafted on PEVA

The variation of AcSa released versus the initial amount of AcSa grafted on PEVA was followed during 3, 24, and 48 h of the release process at pH 1, 3, 5, and 7. The profiles of Figures 7–9 showed clearly a minimum and a maximum of AcSa release except at pH 3 during 48 h of the release process, where only a maximum was localized at 1.73 mg of the total amount of AcSa incorporated in hydrogel (Figure 9). Outside this previous exception, the minimum of aspirin released shifted from 1.55 to 1.73 mg depending on the pH of the media, while the maximum of acetylsalicylic acid released was localized at 2.64 mg of the total amount of AcSa in PEVA-*graft*-AcSa hydrogel except at pH 3 during 48 h of the release process. On the light of these results, it was also revealed that at any duration the lower amount of AcSa released was obtained when the pH of the

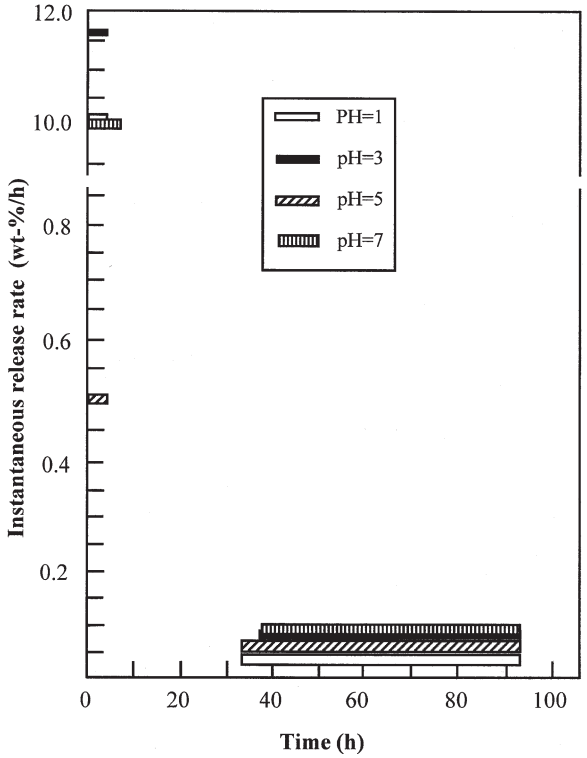


**Figure 6.** Stability zone of instantaneous rate of AcSa released from AcSa-*graft*-PEVA hydrogel ($H_5$) versus the time at 37°C.

media was 1, while the higher AcSa amount released from hydrogel was reached at pH 7. This fact can be explained by the hydrophilic–hydrophobic balance of hydrogel. Indeed at acidic pH. the reaction of esterification is favored and consequently this fact drives to the increase of AcSa amount grafted and by this way decreases the swelling degree of hydrogel in the media, because the ester formed during the esterification reaction

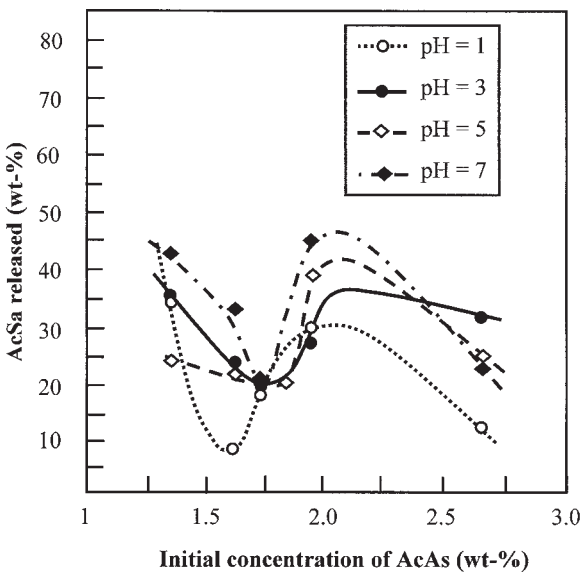


**Figure 7.** Acetylsalicylic acid released from PEVA-*graft*-AcSA hydrogels versus the total initial concentration of AcSa at different pH during 3 h.

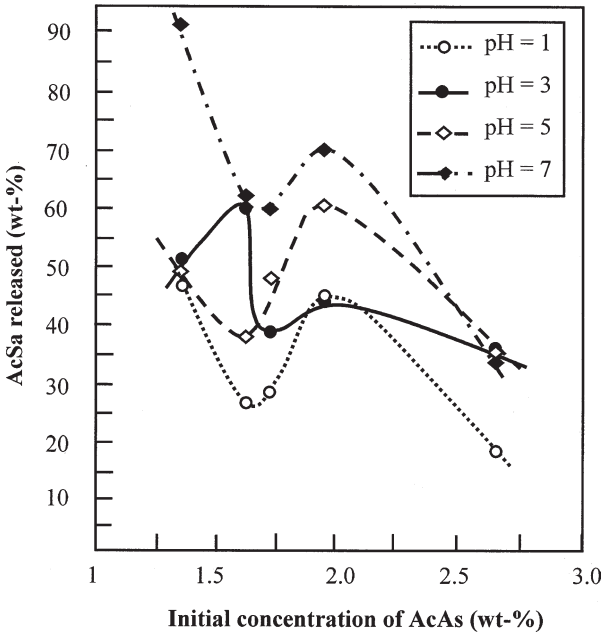


**Figure 8.** Acetylsalicylic acid released from PEVA-*graft*-AcSA hydrogels versus the total initial concentration of AcSa at different pH during 24 h.

becomes little soluble. On the reverse, at a neutral pH the retro-esterification reaction is favored and consequently leads to increase the formation of free acetylsalicylic acid. By this way the swelling degree increases and drives to increase the release of AcSa formed.

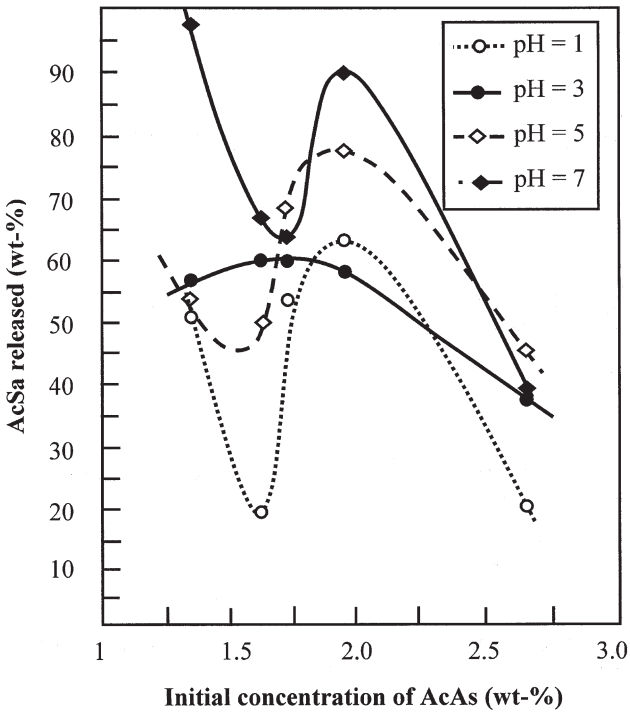


**Figure 9.** Acetylsalicylic acid released from PEVA-*graft*-AcSA hydrogels versus the total initial concentration of AcSa at different pH during 48 h.

## CONCLUSION

Very interesting results are obtained from this investigation. Acetylsalicylic acid can be grafted easily on poly(vinylalcohol-*co*-ethylene) by esterification reaction. The conversion rate in the polymer grafted is controlled by removing water produced during the reaction under reduced pressure. This method compared with those of encapsulation permits to obtain a material characterized by a perfect distribution of acetylsalicylic acid in the polymer. The corresponding hydrogel can be easily obtained by the same reaction using oxalic acid as a crosslinking agent. The acetylsalicylic acid released from poly(vinylalcohol-*co*-ethylene-*graft*-acetylsalicylic acid) in an aqueous media occurred by retroesterification reaction, notably at a neutral pH. The results obtained indicated that the maximum amount of AcSa released (more than 92 wt %) reached pH 7 during a period of 60 h with hydrogels containing initially 1.95, 1.38, and 1.62 mg of a total amount of AcSa. The study of the release rate indicated that the stability in the AcSa-release rate during the time depended on the initial amount of AcSa incorporated in PEVA and the pH of media. The effect of the initial amount AcSa grafted on PEVA revealed that the higher amount of AcSa released was obtained when the pH of media was 7, while the lower AcSa amount released from hydrogel was reached at pH 1. These results were found to be satisfactory and could be applied to a wide range of drugs containing carboxylic groups. The results obtained seemed to be very important in the drug-release domain, because these hydrogels were able to release the greatest amount of aspirin directly in the intestines (neutral pH) and not in the stomach (pH 1).

## ACKNOWLEDGMENTS

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## REFERENCES

1. Hua, Y.; Grainger, D. W. *J. Appl. Polym. Sci.* **1993,** *49*, 1553.
2. Otaka, K.; Inomata, H.; Konno, M.; Saito, S. *Macromolecules* **1990,** *23*, 283.
3. Inomata, H.; Goto, S.; Saito, S. *Macromolecules* **1990,** *23*, 4887.
4. Ilvasky, M.; Hrouz, T.; Ulbrich, K. *Polym. Bull.* **1982,** *7*, 107.
5. Senel, S.; Isik-Yuruksoy, B.; Cicek, H.; Tuncel, A. *J. Appl. Polym. Sci.* **1997,** *64*, 1775.
6. Yan, C. H.; Kitano, H.; Nakamura, K. *Makromol. Chem. Macromol. Chem. Phys.* **1991,** *192*, 12.
7. Varshosaz, J.; Koopaie, N. *Iran. Polym. J.* **2002,** *1*, 123.
8. Pal, K.; Banthia, A.K.; Majumdar, D. K. *J. Biomater. Appl.* **2006,** *21*, 75.
9. Orienti, I.; Trere, R.; Luppi, B.; Bigucci, F.; Cerchiara, T.; Zuccari, G.; Zecchi, V. *Arch. Pharm.* **2002,** *335*, 89.
10. Young, T. H.; Chung, W. Y.; Wei, C. W.; Tang, C. Y. *J. Membr. Sci.* **2001,** *191*, 199.
11. Tomita, K.; Kojoh, K.; Suzuki, A. *J. Ferment. Bioeng.* **1997,** *84*, 400.
12. Mejia, A.I.; Lopez, B.L.; L Sierra, L. *Mater. Res. Innovat.* **2001,** *4*, 148.
13. Lopez, B.L.; Mejia, A.I.; Sierra, L. *Polym. Eng. Sci.* **1999,** *39*, 1346.
14. Mejia, A.I.; Lopez, B.L.; Muler, A. *Macromol Chem. Phys. Symp.* **1999,** *148*, 131
15. Bayer HealthCare AG. Aspirin: History & Structure, A Central Source of Technical & Medical Data on the Use of Aspirin, Aspirin Foundation, Available at http://www.aspirin-foundation.com.
16. Reynolds, J. E. Analgestic anti-inflammatory and antipyretic. The Complete Drug Reference, 32nd ed.; Martinale, Parfitt K: MA, **1999; p 2**
17. Peter Childs, E., The Centenary of Aspirin: Wonder Drug of the Twentieth Century; Available at http://www.ul.ie/.
18. Raderick, P. J.; Wilkes, H. G.; Meade, T. W. *Br. J. Clin. Pharmacol.* **1993,** *35*, 219.
19. Holliday, W. M.; Berdrick, M.; Bell, S. A.; Kiritsis, G. C. US Pat. 3,488,418 ( **1970).**
20. Powel, T. C.; Steinte, M. E.; Yoncoskie, R. A. US Pat. 3.415,715,758 ( **1968).**
21. Dash, V.; Mishra, S. K.; Singh, M.; Goyal, A. K.; Rath, G. *Sci. Pharm.* **2010,** *78*, 93.
22. Amperiadou, A.; Georgarakis, M. *Int. J. Pharm.* **1995,** *115*, 1.
23. Takada, S.; Kurokawa, T.; Iwasa, S. US Pat. 6,117,455 (**1995).**
24. Jaya, S.; Durance, T. D.; Wang, R. *Open Biomater. J.* **2010,** *2*, 9.
25. Polk, A.; Amsden, B.; Deyao, K.; Peng, T.; Goosen, M. F. A. *J. Pharm. Sci.* **1994,** *83*, 178.
26. Gonzalez, M.; Rieumont, J.; Dupeyron, D.; Perdomo, I.; Fernandez, E.; Abdon, L.; Castano, V. M. *Rev. Adv. Mater. Sci.* **2008,** *17*, 71.
27. Hazneder, S.; Dortunc, B. *Int. J. Pharm.* **2004,** *269*, 131.
28. Rao, V. M.; Engh, K.; Qiu, Y. *Int. J. Pharm.* **2003,** *252*, 81.
29. Ferrero, C.I.; Bravo, M.; Jimenez, R. J. *Controlled Release* **2003,** *92*, 69.
30. Chen, W.; Lu, D. R. *J. Microencapsul.* **1999,** *16*, 551.
31. Gabor, F.; Ertl, B.; Wirth, M.; Mallinger, R. *J. Microencapsul.* **1999,** *16*, 639.
32. Jenquin, M. R.; Liebowitz, S. M.; Sarabia, R. E.; McGinity, J. W. *J. Pharm. Sci.* **1990,** *79*, 811.
33. Gavhane, Y. N.; Shinde, V. R.; Mudannapatil, P. B.; Yadav, A. V. *Arch. Pharm. Sci. Res.* **2009,** *1*, 75.
34. Zhuang, Y.; Yang, H.; Wang, G.; Zhu, Z.; Song, W.; Zhao, H. *J. Appl. Polym. Sci.* **2003,** *88*, 724.
35. Taranti, P. A.; Andreopoulus, A. G. In Proceeding of the 8th Polymers for Advanced Technologies International Symposium, Budapest, Hungary, 13–16 Sep **2005.**