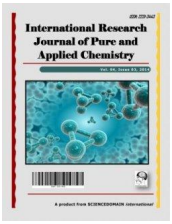

International Research Journal of Pure & Applied Chemistry
12(4): 1-10, 2016, Article no.IRJPAC.28989
ISSN: 2231-3443, NLM ID: 101647669

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Synthesis and Characterization of PVA-Gelatin Hydrogel Membranes for Controlled Delivery of Captopril

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IRJPAC/2016/28989
Editor(s):
(1) Chunyang Cao, State Key Laboratory of Bioorganic and Natural Product Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China.
Reviewers:
(1) Haroon Rahim, Sarhad University of Science and Information Technology Peshawar, Khyber Pakhtunkhwa, Pakistan.
(2) Mona Samir Hashem Mahmoud, National Research Centre, Egypt.
Complete Peer review History: http://www.sciencedomain.org/review-history/16347

Original Research Article

Received 16th August 2016
Accepted 10th September 2016
Published 27th September 2016

ABSTRACT

Many biomedical applications including controlled drug delivery systems have been developed based on hydrogel technologies. Different composite hydrogels including synthetic and natural polymers can be produced to controllable systems in drug deliver application.
In this study, poly vinyl alcohol (PVA)-Gelatin hydrogel membranes were prepared by the esterification reaction between hydroxyl groups of PVA and carboxyl groups of Gelatin to deliver Captopril as a model of drug. Captopril was successfully loaded into PVA-Gelatin hydrogel membrane in different ration of Gelatin (10:1, 10:2, 10:3, 10:4, 10:5, 10:6, 10:7, and 10:8). The prepared hydrogel membranes were characterized by Fourier Transforms Infrared Spectroscopy (FT-IR) and Scanning Electron Microscopy (SEM). The effects of different process parameters, like percentage of Gelatin, size distribution, swelling behavior and in vitro drug releasing from hydrogel membrane in different phosphate buffer solutions pH (7.1 and 3.9) were studied. The models of kinetics of releasing drug were investigated by using different types of mechanisms (Zero-order, First order, Higuchi's model and Korsmeyer-Peppas Model).

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Keywords: Poly vinyl alcohol; gelatin; Captopril; drug delivery system; esterification.

1. INTRODUCTION

An interesting method to obtain new materials is by blending of natural polymers with synthetic ones in which the former properties are improved to be suitable for specific applications [1]. Gelatin, among natural polymer, has a vital position due to its versatility in enhancing drug delivery systems by blending with synthetic polymers like poly vinyl alcohol (PVA) to be used for more applications [2].

Gelatin can obtained by the thermal denaturation of collagen from the skin and bones of animals and rarely fish scales. Mainly, it contains the residues of three amino acids: glycine (arranged every third residue), 4-hydroxyproline and proline in its structure [3]. The Gelatin, naturally, possesses excellent biocompatibility and forms a membrane at ambient temperature [4].

Usually the Gelatin manufacture is carried out by acid pre-treatment (type A) or alkali pre-treatment (type B) from bovine or porcine skin or bone [5]. The hydrolytic degradation shows that Gelatin extractions have different physical and chemical properties during process [6]. Thus, seeking for edible, pharmaceutical and photographic uses and for medical application, it has focused on scientific interest [7].

Poly vinyl alcohol (PVA) is a nontoxic hydrophilic polymer. Its properties like easy process ability, biocompatibility and biodegradability play an important role in designing pharmaceutical, biomedical devices and drug delivery systems [8,9]. Because of the hydrogels ability to absorb and retain fluids and bioactive materials, many researchers were attracted to work with them [10]. Poly vinyl alcohol (PVA) has a lot of hydroxyl groups, which allows it to react with many types of functional groups. This advantage makes it suitable as a drug delivery polymer [11].

Captopril is the generic name for the medicine Capoten. It is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II [12]. Captopril has molecular weight (217.29 mol/g) and has the following structure:

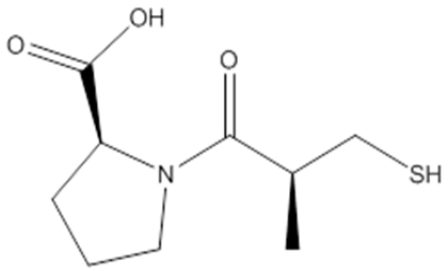

Fig. 1. Structure of Captopril

The aim of this work is to develop biodegradable membranes based on blends of Gelatin and poly vinyl alcohol (PVA) by esterifying the hydroxyl groups of PVA with the carboxyl groups of Gelatin. As it tries to recognize some of their properties including degree of swelling, FT-IR, morphology (SEM) and size distribution. In addition, loading Captopril as a drug model and releasing from the membranes were investigated.

2. MATERIALS AND METHODS

2.1 Materials

Poly vinyl alcohol ($M.W_t$. 85000 mole/g) was obtained from BDH chemicals company, UK. Gelatin was purchased from Sigma-Aldrich chemicals company, UK. Captopril was obtained from Awamedica pharmaceutical company, Erbil, Iraq. All other chemicals were used without any further purification.

2.2 Preparation of PVA-Gelatin Hydrogel Membranes

PVA-Gelatin hydrogel Membranes were prepared by esterification of hydroxyl groups of PVA with carboxyl groups of gelatin [13]. 1 g of PVA was dissolved in distilled water (D.W.) at (70-80°C) with stirring until a clear solution was obtained. Different amounts of Gelatin (according to Table. 1) were dissolved in D.W. with stirring at (30-35°C) until appearing the clear solution and then gently adding them to the previously prepared PVA solution with stirring (200 rpm) to form PVA-Gelatin solution.

Esterification between PVA and Gelatin was initiated in acidic medium by adding conc. hydrochloric acid. PVA-Gelatin homogenous

solution was converted to membrane by solution casting method on petri dish plates. The PVA-Gelatin membranes were vacuum dried at 30°C.

The membranes were carefully removed and immersed in sodium hydroxide solution (2M), washed with hot and cold ionized water and then vacuum dried at 30°C.

Table 1. Combination of PVA-Gelatin hydrogel membranes

No. of sample	PVA: Gelatin ratio	Conc. HCl (µml)
1	10:1	100
2	10:2	120
3	10:3	140
4	10:4	160
5	10:5	180
6	10:6	200
7	10:7	220
8	10:8	240

2.3 Fourier Transforms Infrared Spectroscopy (FT-IR)

FT-IT spectroscopy (in the spectral region between 450-4000 cm^{-1}) type (Perkin Elmer model-spectrum one) was used to assess the polymer chemical groups (PVA, Gelatin and PVA-gelatin hydrogel membranes) and investigate the formation of esterification between PVA-Gelatin.

2.4 Degree of Swelling

The degree of swelling of the prepared PVA-Gelatin hydrogel membranes (cut 2*2 cm) was determined by keeping the later in 50 ml phosphate buffer solutions (pH 7.1 and 3.9) and recording variation in their weight (W_t) in comparison to their initial weight (W_0). The percentage degree of swelling is calculated by using equation (1):

$$(Sw\%) = \frac{W_t - W_0}{W_0} * 100 \quad (1)$$

Where W_t and W_0 are the weights of membrane at time t and zero time there is swelling in hydrogel membrane respectively.

2.5 Morphology Study of PVA-Gelatin Membranes

The morphology study of PVA-Gelatin hydrogel membranes after and before releasing drug have been investigated by using a Scanning Electron Microscope (SEM) type (QUANTA 450) (SEM micrographs were performed at Soran University, Soran, Iraq).

2.6 Loading Drug

The loading of Captopril on PVA-Gelatin hydrogel membranes were carried out by solution casting method. PVA-Gelatin solution acidified by conc. HCl was prepared. Simultaneously, Captopril was added to the blend under magnetic stirring for homogenous dispersion. The dispersion obtained was converted to membrane by solution casting method on petri dish plates.

2.7 Determination of Percentage Drug Entrapment

100 mg of hydrogel membrane was crushed in an agate mortar, then place it in 100 ml of phosphate buffer solutions (pH 7.1 and 3.9) with stirring to release the drug dispersed inside the holes of membrane. Then it was sonicated for 2 h and filtered to remove debris. The absorbance was measured by using UV-VIS-PC. Quantitative estimation of Captopril was calculated by using equation obtained by liner regression analysis of the calibration data of the drug in phosphate buffer solutions (see Table 2). The drug loaded into the hydrogel membrane was estimated using equation (2):

$$PDL = \frac{\text{Actual Drug loading}}{\text{Theoretical Drug loading}} * 100 \quad (2)$$

Where PDL = percentage Drug loading

Table 2. Targeted and actual drug loading in PVA-Gelatin hydrogel membranes in different phosphate buffer solutions

pH medium	Targeted drug loading %	Actual drug loading%	Drug loading efficiency
7.1	5	3.9	78
3.9	5	3.1	62

2.8 *In vitro* Releasing Study

The release studies were conducted by keeping an exact weight (100 mg) of Captopril loaded PVA-Gelatin hydrogel membranes in 50 ml of different phosphate buffer solutions (pH 7.1 and 3.9) for different time intervals at 37°C±2 in constant temperature water bath (Lab Tech LSB-015S). The amount of drug released was

analyzed by using UV-VIS-PC spectrophotometer (Perkin Elmer Lambda) at 279 nm.

Each release experiment was carried out in triplicate and averages were calculated.

2.9 Determination of Calibration Curve

Calibration curve of Captopril was prepared by using different phosphate buffer solutions (pH 7.1 and 3.9) in the concentration range (5-30 mg/ml). The drug concentration was analyzed by using UV-VIS-PC spectrophotometer (Perkin Elmer Lambda) at 279 nm.

2.10 Study of Drug Release Kinetics

Kinetics of drug release (Captopril) from PVA-Gelatin hydrogel membranes are tested by using Zero order rate, First order rate, Higuchi and Korsmeyer-Peppas Model drug release kinetic models.

3. RESULTS AND DISCUSSION

3.1 Fourier Transforms Infrared Spectroscopy (FT-IR)

The FT-IR spectra of PVA showed a broad peak around 3457 cm^{-1} indicating stretching of –OH group and peaks at 2938 cm^{-1} and 2856 cm^{-1} due to -C-H stretching. The FT-IT spectra of Gelatin showed a peak at 3435 cm^{-1} due to –N-H stretching of amide, –C=O stretching at 1935 cm^{-1} and –C-H stretching at 2922 cm^{-1}. The FT-IR spectra of the PVA-Gelatin hydrogel membrane esterified showed the peak of –C=O of Gelatin at 1635 cm^{-1} shifted to 1731 cm^{-1}, to indicate the esterification of PVA and Gelatin. The peak around 3410 cm^{-1} points the presence of –OH group with polymeric association and a secondary amide. The FT-IR results suggest a complete esterification of the carboxylic acid of Gelatin.

3.2 Degree of Swelling

Trying to specify the experimental conditions for optimum loading and releasing of Captopril from PVA-Gelatin hydrogel membranes, the swelling behavior of PVA-Gelatin membrane was investigated at different time intervals in different phosphate buffer solutions (pH 7.1 and 3.9) with incubated at 37°C±1.

Sample 7 of PVA-Gelatin hydrogel membrane showed a maximum degree of swelling (189 W_t %) at pH (7.1), and sample 8 showed a maximum degree of swelling (69 W_t %) at pH (3.9) within the first hour, while sample 1 showed (10 W_t %), sample 3 (110 W_t %), sample 4 (148 W_t %) and sample 8 (187 W_t %) all at pH 7.1. However, sample 1 showed (6 W_t %), sample 3 (26 W_t %), sample 5 (44 W_t %) and sample 7 (50 W_t %) at pH (3.9).

Degree of swelling of sample 3 was increased to (160 W_t %) while sample 5 was increased to (164 W_t %). Sample 7 showed again a maximum swelling (291.6 W_t %) at pH (7.1). Whereas, sample 2 showed (42.8 W_t %), sample 5 (73.3 W_t %) and sample 8 showed a maximum swelling again (104.3 W_t %) at pH (3.9) within the first four hour.

After the first 12 h, the degree of swelling of sample 1 was increased to (85.7 W_t %), sample 5 to (182.6 W_t %), sample 7 to (358.3 W_t %) and sample 8 showed a maximum degree of swelling (434.7 W_t %) at pH (7.1), while sample 2 showed (88.5 W_t %), sample 4 (155.22 W_t %) and sample 8 showed again maximum degree of swelling (291.3 W_t %) at pH (3.9).

Eventually 24 h later, the degree of swelling of sample 2 was increased to (157 W_t %) at pH (7.1) while (100 W_t %) at pH (3.9). For sample 4 it was increased to (194 W_t %) at pH (7.1) while (163.1 W_t %) at pH (3.9), sample 7 (416.6 W_t %) at pH (7.1) while (325 W_t %) at pH (3.9), sample 8 showed maximum swelling comparing other samples (569.5 W_t %) at pH (7.1) while (378.2 W_t %) at pH (3.9).

Figs. 2 and 3 show the swelling behavior of PVA-Gelatin hydrogel membranes in different phosphate buffer solution pH (3.9) and pH (7.1)

The study clearly indicates that sample 8 of PVA-Gelatin hydrogel membrane was suitable for loading and releasing of Captopril.

3.3 Scanning Electron Microscopy (SEM)

SEM images and surface morphology of PVA-Gelatin hydrogel membrane samples were investigated.

The SEM images of the hydrogel membrane Fig. 4 (A,B,C,D) (before releasing drug) show clearly the surface morphology of the hydrogel membrane. Fig. 4 (A) shows the homogenous, uniform and smooth composite morphological surface. Fig. 4 (B), the SEM image shows the

cross section of the hydrogel membrane which appears the undulant and tight surface, with porous and cohesive composite as a result to the esterification reaction between PVA and Gelatin. A closer view clears that this surface contains some deep and long holes. At higher magnification, Fig. 4 (C,D) shows the suitability of these holes for penetrating water into the polymeric structure. Thus, they are useful for more water uptake.

However, Fig. 5 (A,B,C,D) show the SEM images of PVA-Gelatin hydrogel membrane (after releasing drug).

Fig. 5 (A) shows highly uneven folds exist inside and in between the membrane which means that the hydrogel could be present in elastic form, with the help of its ability to form the three-dimensional structure easily. In Fig. 5 (B), the image verifies the presence of these folds, which were longitudinal and deep. Furthermore, degradation resulted in causing some Protrusions. The cross section, Fig. 5 (C) of the hydrogel membrane shows the inner composite of the membrane, which was similar to the 3D composition with some big size holds.

As a higher magnification, Fig. 5 (D) clears the polymeric structure after releasing drug. Such a thing refers to the degradation of the hydrogel membrane, which is supported by the fact that 53%W_t. degradation hydrogel membrane was happened after 21 days.

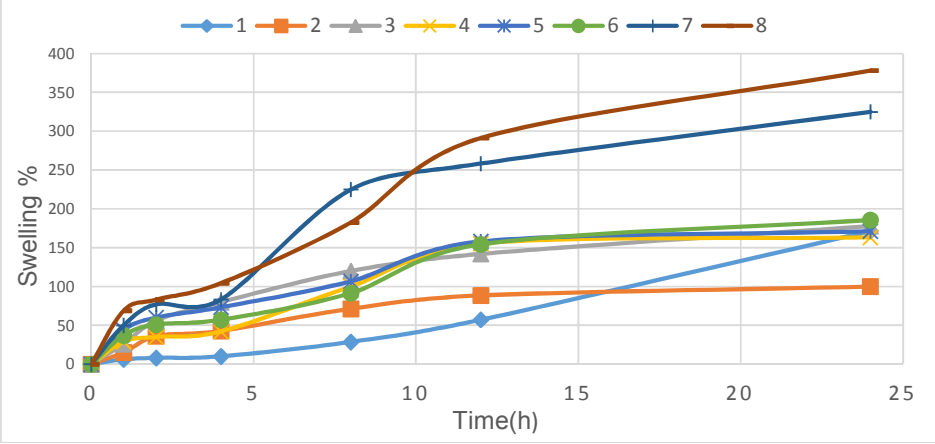

Fig. 2. Degree of swelling of PVA-Gelatin hydrogel membranes in phosphate buffer solution pH (3.9)

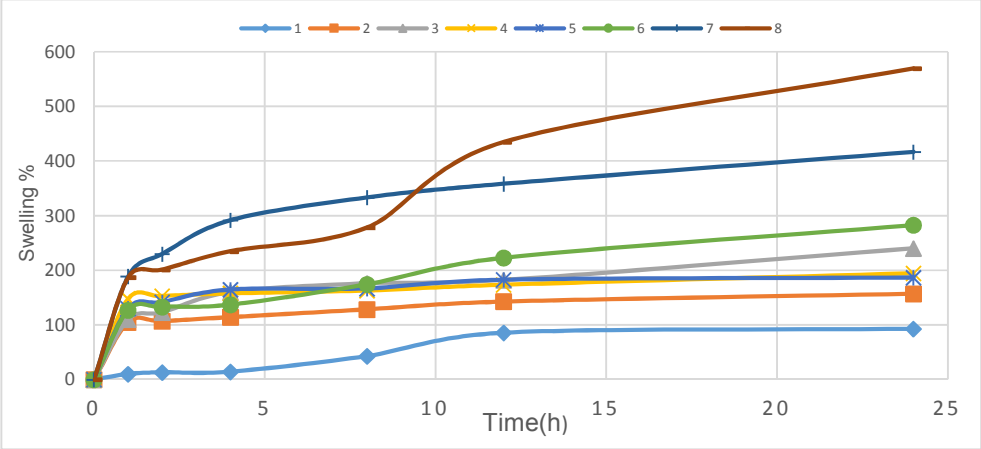

Fig. 3. Degree of swelling of PVA-Gelatin hydrogel membranes in phosphate buffer solution pH (7.1)

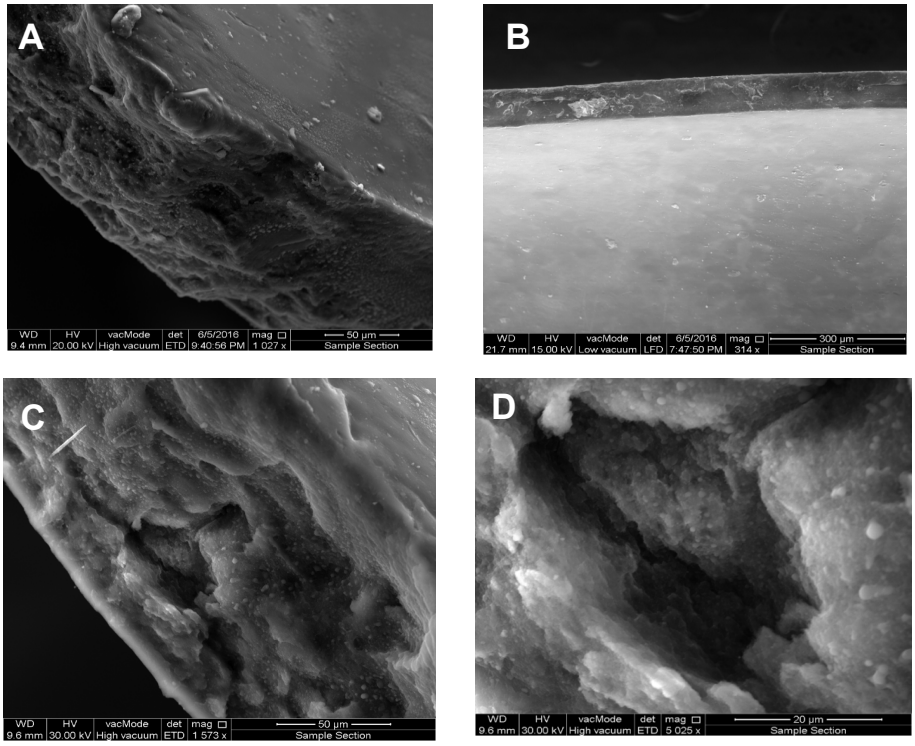

Fig. 4. SEM of PVA-Gelatin hydrogel membrane (A,B.C,D) before releasing drug

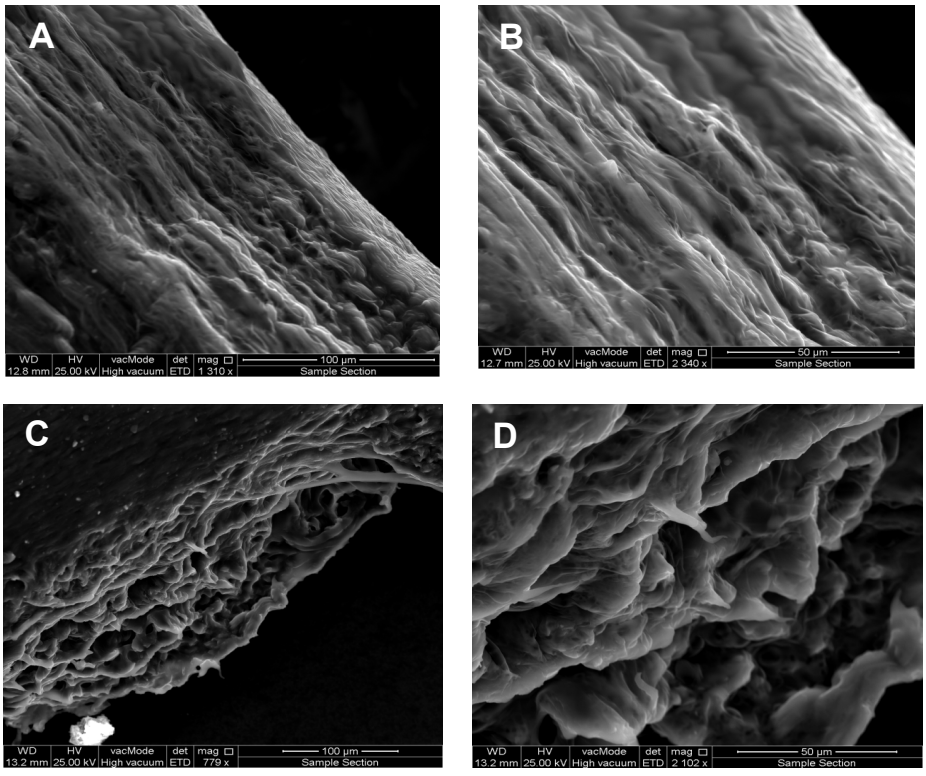

Fig. 5. SEM of PVA-Gelatin hydrogel membrane (A,B.C,D) after releasing drug

3.4 Study of Drug Releasing

The release of Captopril from PVA-Gelatin hydrogel membranes was investigated at 37°C±1 in different phosphate buffer solutions pH (7.1 and 3.9). It was generally noticed that there is an immediate release of Captopril at the time of immersing hydrogel membrane loaded with drug in the release medium. This might be due to the surface of the drug on the membrane. This explanation is supported by the fact that this immediate release depends on the pH of the medium.

Fig. 6 shows the percentage release curve of Captopril from PVA-Gelatin hydrogel membrane. It can be seen that Captopril released from PVA-Gelatin membrane was (84.09%) at pH (7.1) and (66%) at pH (3.9) within 48 h. This suggests that Captopril release properties of PVA-Gelatin hydrogel are pH sensitive. This can be correlated with degree of swelling of PVA-Gelatin membranes as in Figs. 2 and 3, where the swelling was increased when pH of the medium has changed from acidic to neutral. At neutral medium pH (7.1), the $-COO^-$ group in the PVA-Gelatin hydrogel membrane led to higher swelling and Captopril release from the prepared hydrogel membrane.

3.5 The Kinetic of Drug Release from PVA-Gelatin Hydrogel Membrane

For the characterization of the release kinetics studies and to determine the release mechanism of drug, the results of in vitro studies were fitted with several kinetics models as follows.

Zero order rate equation: $Q_t = Q_0 + K_0 t$

Where Q_t is the amount of drug dissolved in time t, Q_0 is initial amount of drug in buffer solution, and K_0 is zero order release constant.

First order rate equation: $\log C = \log C_0 - K_t/2.303$

Where C_0 is the initial concentration of drug, K is first order release constant, and t is time.

Higuchi's model: $Q = K_H t^{1/2}$

Where Q is the amount of drug released in time t per unit area, K_H is Higuchi dissolution constant.

Korsmeyer -Peppas Model $M_t/M_\infty = Kt^n$

Where M_t / M_∞ is fraction of drug released (first 60% drug release) at time t, k is the rate constant and n is the release exponent which is an important indicator of the mechanism of drug transport from the hydrogel membrane. A value of $n \leq 0.45$ indicates that drug release is controlled by Fickian diffusion, whereas a value of $n \geq 0.89$ suggests that drug release is dominated by an erosion mechanism. For values $0.45 < n < 0.89$, the release is described as anomalous, implying that a combination of diffusion and erosion contributes to the control of drug release.

When the obtained dissolution data were fitted into the zero-order kinetic model, it is evident from (Figs. 7 and 8 and Table 3) that the plots were curvilinear for all formulation (different phosphate buffer solutions pH 3.9 and 7.1).

As the small regression values, suggest that the release kinetic did not follow the zero-order. On the other hand, the dissolution results obtained were found to fit well with the first-order kinetic model. It is clearly evident from Figs. 7 and 8 as well as regression parameters illustrated in Table 3 that a high correlation coefficient was obtained with all the r^2 values close to unity. As well as, these r^2 values of first-order kinetic equation (0.4525 at pH 3.9 and 0.4453 at pH 7.1) were higher than those obtained for zero-order kinetic equation (0.4131 at pH 3.9 and 0.4103 at pH 7.1). These data suggest strongly a diffusion Captopril release mechanism from PVA-Gelatin hydrogel.

Beside the first-order mechanism model, the mechanism of drug release from PVA-Gelatin hydrogel membranes was evaluated by fitting the dissolution data of the drug release profiles to Higuchi's square root model equation of diffusion. It can be observe from Figs. 7 and 8 as well as Table 3 that a semi-linear relationship was obtained with all the formulation and r^2 values were (0.7396 at pH 3.9 and 0.7411 at pH 7.1) which indicated that the release of Captopril from PVA-Gelatin hydrogel was through the diffusion mechanism.

Furthermore, to determine whether the dissolution was also involved in the drug release from PVA-Gelatin hydrogel, the dissolution data of drug release profile were fitted to Korsmeyer-Peppas Model. The exponent n values were (0.447 at pH 3.9 and 0.435 at pH 7.1) indicated that the mechanism was Fickian diffusion model. This implies that dissolution might have also

occurred in the release of drug from PVA-Gelatin hydrogel. So, the release of Captopril from PVA-Gelatin hydrogel was attributed to both diffusion and dissolution mechanisms.

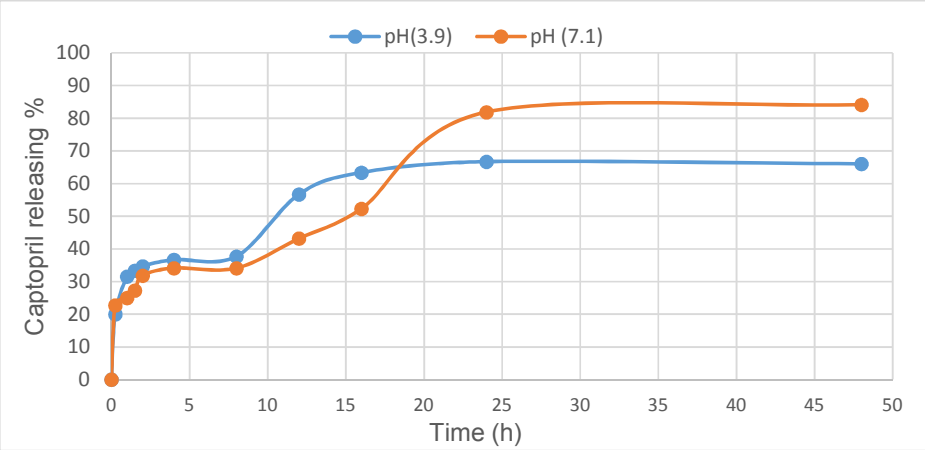

Fig. 6. Captopril releasing from PVA-Gelatin hydrogel membranes in different phosphate buffer solutions pH (3.9 and 7.1)

Table 3. Kinetics data of Captopril release from PVA-Gelatin hydrogel membrane in different phosphate buffer solutions pH (3.9 and 7.1)

pH medium	Zero-order		First-order		Higuchi's		Korsmeyer-Peppas
	r^2	K_0	r^2	K_0	r^2	K_0	n
3.9	0.4131	18.407	0.4525	1.906	0.7396	9.2461	0.447
7.1	0.4103	17.428	0.4453	1.9118	0.7411	8.7444	0.435

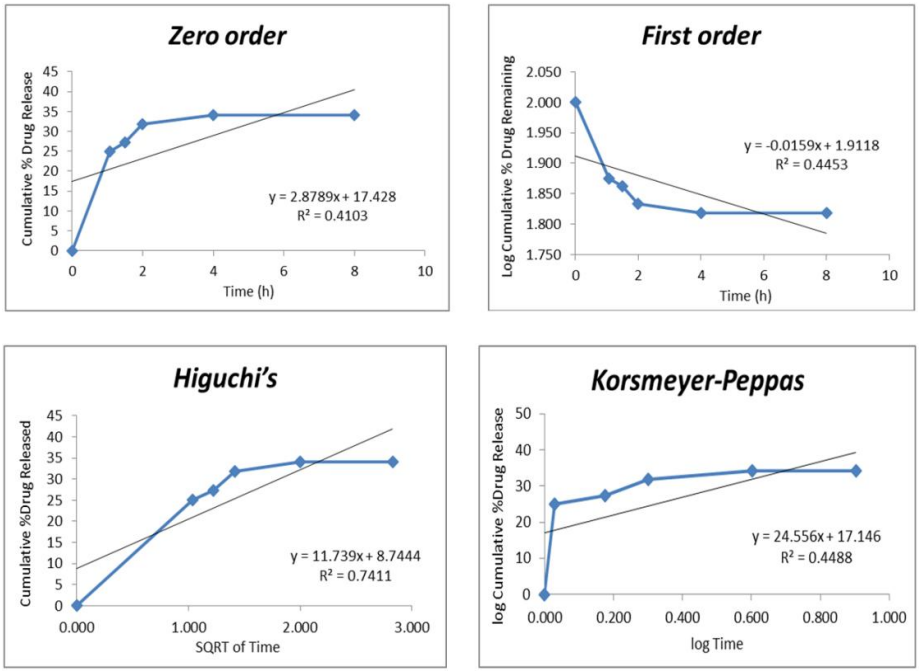

Fig. 7. Comparative plots of in vitro release profile, Zero order release kinetic, First order release kinetic, Higuchi's (SQRT) release kinetic and Korsmeyer-Peppas Model kinetic in phosphate buffer solution at pH 7.1

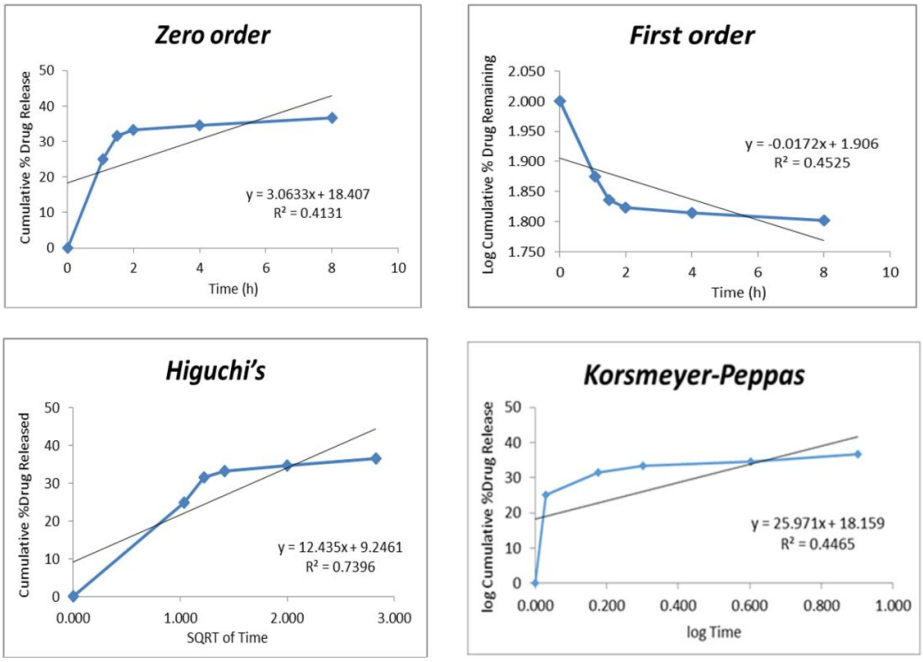

Fig. 8. Comparative plots of in vitro release profile, Zero order release kinetic, First order release kinetic, Higuchi's (SQRT) release kinetic and Korsmeyer-Peppas Model kinetic in phosphate buffer solution at pH 3.9

4. CONCLUSIONS

Hydrogel membranes for controlled delivery of Captopril were prepared by the esterification between the hydroxyl groups of poly vinyl alcohol (PVA) and the carboxyl groups of Gelatin. The prepared hydrogel membranes were characterized by degree of swelling, FT-IR spectroscopy and surface morphology (SEM). The loading and releasing characteristics of hydrogel membranes were evaluated.

The (10:8) PVA-Gelatin hydrogel membrane prepared was more efficient in controlled releasing of Captopril than other percentages of PVA-Gelatin hydrogel membranes and showed 53%W_t. degradation within 21 days. The PVA-Gelatin hydrogel membranes formed by esterification reaction between PVA and Gelatin were nontoxic and biodegradable.

ACKNOWLEDGEMENT

Authors are thankful to the research center, Soran University, Kurdistan Region, Iraq, for providing (SEM) facility for research work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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