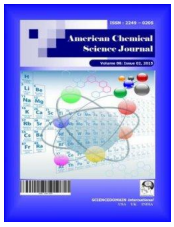

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Preparation and Characterization of PVA-NaAlg Interpenetrating Polymer Network (IPN) Hydrogel for Controlled Delivery of Carbidopa

Alarqam Zyaad Tareq[1*]

[1]*Department of Chemistry, Faculty of Science, University of Zakho, Zakho, Iraq.*

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Polymeric drug delivery systems are new developed technology. They can be used to support patient's compliance. They can help to maintain uniform drug levels and increase the safety margin for high-potency drugs. Then, they decrease the number of daily doses.
Thus, in this study, Poly vinyl alcohol (PVA)-Sodium alginate (NaAlg) interpenetrating polymer network (IPN) hydrogels were prepared by using Glutaraldehyde as a crosslinked. The model drug (Carbidopa) was delivered by using emulsification / solvent-evaporation method. Carbidopa was successfully loaded into PVA-NaAlg IPN hydrogels. The prepared IPN hydrogels were characterized by Fourier Transforms Infrared Spectroscopy using (FT-IR) and Scanning Electron Microscopy (SEM). The effects of different process parameters, like degree of swelling and *In vitro* drug releasing of IPN hydrogel 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 Hixson-Crowell model).

Keywords: Poly vinyl alcohol; sodium alginate; carbidopa; drug delivery system; interpenetrating polymer network (IPN).

**Corresponding author: E-mail: alarqam.tareq@uoz.edu.krd;*

1. INTRODUCTION

Recently, the polymer science has developed to invent new types of drug delivery systems [1]. One of these systems is interpenetrating polymer network (IPN). This newly developed bioactive material is an emerging tool in pharmaceutical industry. IPN plays an essential role in polymer drug delivery systems because of its improved biocompatibility and safety profiles they offer as a result to their physical characteristics like its good swelling properties [2]. Its characteristics are very useful in various domains of drug delivery. IPN improves the solubility of hydrophobic drugs and drug targeting a specific tissue. As, it improves the bioavailability and biodegradability [3].

Any chemical modification or combination of polymers can be directly come up with new materials with potential applications in several fields [4]. For instance, biomaterials' characteristics can be improved by the combination of synthetic polymers and biological polymers. Whereas synthetic polymers have good physicochemical and mechanical properties but not sufficient biocompatibility, biological polymers are characterized by their good biocompatibility but their mechanical properties are often limited [5]. Therefore, a successful combination has been by blending sodium alginate and poly vinyl alcohol (PVA).

Sodium alginate (NaAlg) is a water soluble linear polysaccharide extracted from brown sea weed and consists of alternating blocks of 1-4 linked α-L-guluronic and β-D-mannuronic acid residues [6]. Reportedly, Sodium alginate is characterized to be mucoadhesive, biodegradable and biocompatible and has potential for numerous pharmaceutical and biomedical applications such as drug delivery systems and cell encapsulation [7].

Poly vinyl alcohol (PVA) is produced by polymerizing vinyl acetate to poly vinyl acetate (PVAc), followed by hydrolyzing of PVAc to PVA. The reaction of this hydrolysis could not be completed resulting in polymers with a certain degree of hydrolysis that depends on the extent of the reaction [8]. Since, it is nontoxic, water soluble, biocompatible and biodegradable, this synthetic polymer is more commonly used for drug delivery system and biochemical applications [9].

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white or yellowish-white crystalline compound, slightly soluble in water, with a molecular weight of (244.3 mol/g). It is designated chemically as (2S)-3-(3,4-Dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate. [10] Its structural formula is:

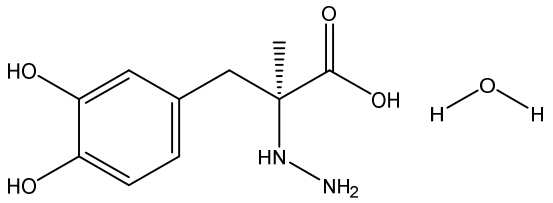


Fig. 1. Structure of Carbidopa

In this study, PVA-NaAlg IPN hydrogels were prepared with Carbidopa as a drug model. The FT-IR, swelling behavior, scanning electron microscopy (SEM), loading and releasing drug from PVA-NaAlg hydrogels were investigated. The drug delivery system was studied at different pH mediums.

2. EXPERIMENTAL

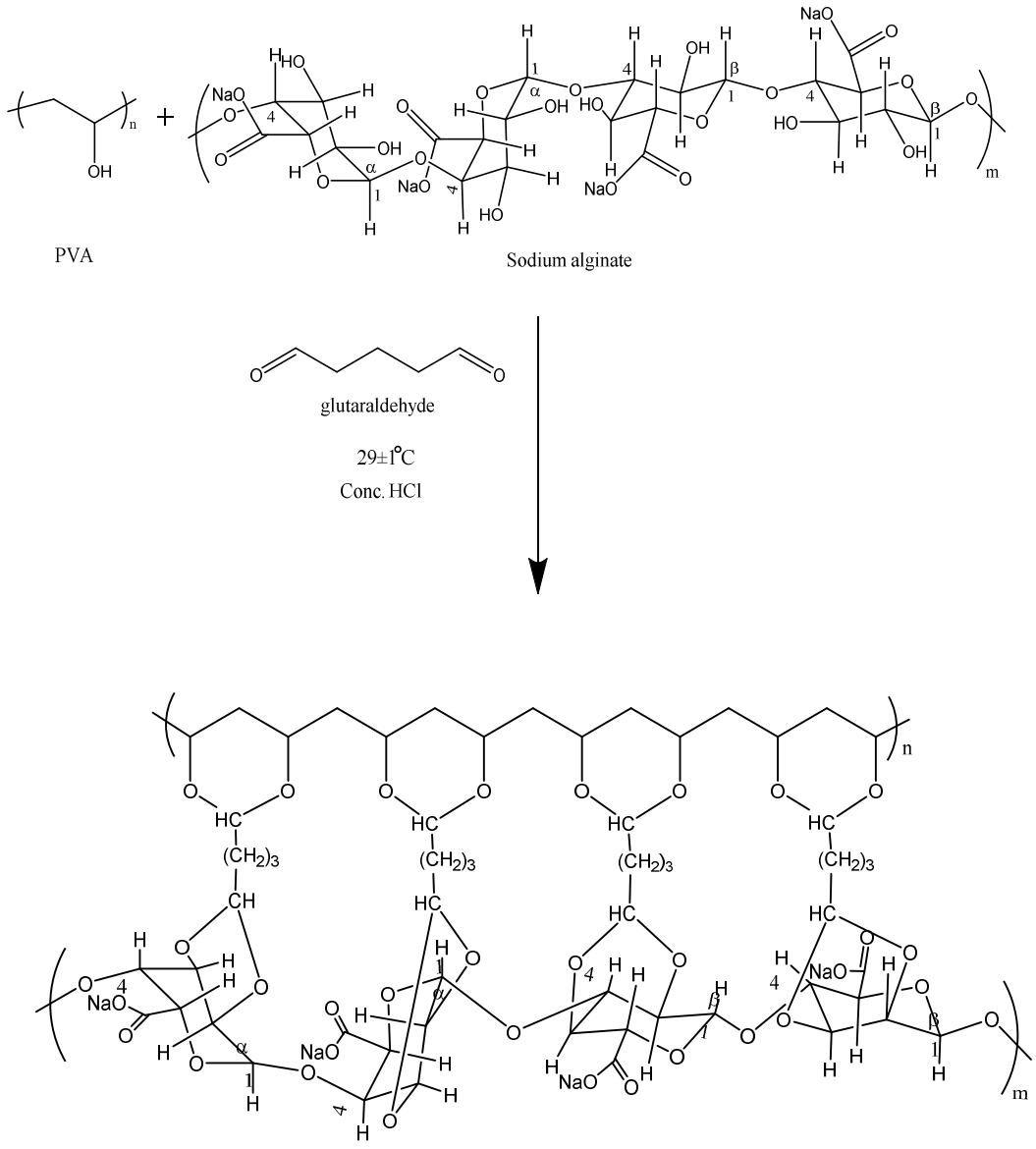
2.1 Materials

Poly vinyl alcohol ($M.W_t$. 85000 mole/g) and sodium alginate (medium viscosity) were purchased from BDH chemical company, UK. Carbidopa was obtained from Awamedica pharmaceutical company, Erbil, Iraq. Glutaraldehyde was supplied by India institute of Tecnology, ROORKE, India. All other chemicals were used without any further purification.

2.2 Preparadtion of PVA-NaAlg IPN Hydrogel

The preparation of the PVA-NaAlg IPN hydrogel has been described elsewhere [11]. In short, (1.2 g) of PVA was dissolved in (15 ml) D.W. with stirring (150 rpm) at 80-85°C until clear PVA solution was obtained. (0.5 g) of NaAlg was dissolved in (10 ml) D.W. with stirring at 30±1°C until appearing clear solution.

NaAlg solution was added carefully to the PVA solution with stirring (150 rpm) for 24 h at r.t to form homogenous solution. (300 µml) of glutaraldehyde was added with (200 µml) conc. HCl with stirring (150 rpm) at 29±1°C until PVA-NaAlg IPN hydrogel was formed as in scheme 1. The formed IPN hydrogel was filtrated, washed with hot and cold water and vacuum dried at 30°C.



Scheme 1. Preparation of PVA-NaAlg IPN hydrogel

2.3 Fourier Transforms Infrared Spectroscopy (FT-IR)

The FT-IR spectrum of poly vinyl alcohol, sodium alginate and PVA-NaAlg IPN hydrogels were obtained by using (Perkin Elmer model-spectrum one) FT-IR spectroscopy (in the region between 450-4000 cm^{-1}).

2.4 Study of Swelling Behavior

To measure the water uptake of PVA-NaAlg IPN hydrogel, (100 mg) of IPN hydrogel was kept in (20 ml) of different phosphate buffer solutions (pH 7.1 and 3.9) and incubated at 37°C. The increase of weight (Wt-W0) of IPN hydrogel at different times intervals compared to the initial weight (W0) of IPN was used to calculate the degree of swelling (Sw) by using equation (1):

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

Where W_t and W_0 are the initial and final weights of the IPN hydrogel.

2.5 Morphology Study of PVA-NaAlg IPN Hydrogel

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

2.6 Determination of Calibration Curve

Calibration curve of Carbidopa was prepared by using different phosphate buffer solutions (pH 7.1 and 3.9) in concentration range (0.1-2.6 mg/ml). The drug concentration was analyzed by using UV-VIS-PC spectrophotometer (Perkin Elmer Lambda) at 305 nm.

2.7 Loading Drug

A modified emulsification / solvent-evaporation method [12] was used for loading Carbidopa on PVA-NaAlg IPN hydrogel. (100 mg) of drug was dissolved in methylene chloride then added to the PVA-NaAlg polymer solution with the required amount of glutaraldehayde as a crosslinked agent and conc. HCl with stirring (150 rpm) to form a stable Oil/water emulsion system at 30±1°C.

Stirring was continued until hydrogels IPN were formed and the methylene chloride was evaporated, then IPN hydrogels were filtered, washed with hot and cold water and vacuum dried at 35°C.

2.8 Determination of Percentage of Drug Entrapment

In order to determine the percentage of drug loading (PDL), (100 mg) of dry PVA-NaAlg IPN hydrogels with loaded drug were crushed in an mortar, stirred with different phosphate buffer solutions pH (7.1 and 3.9) and refluxed at 25°C for 2 h, to ensure the perfect extraction of drug from the IPN hydrogel. When the 2 h finished, the drug was filtered to remove debris and then analyzed by using UV-VIS-PC (Perkin Elmer lambda 25) at a wave length 305 nm. Quantitative estimation of drug was calculated by using equation obtained by liner regression analysis of the calibration data of the drug in different phosphate buffer solutions. Results are showed in (Table 1). The drug loading in IPN hydrogel was estimated by using equation (2):

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

Where PDL = percentage Drug loading

2.9 *In vitro* Releasing Study

The release characteristics of PVA-NaAlg IPN hydrogels were determined by keeping (100 mg) of Carbidopa loaded in IPN hydrogel in (50 ml) of different phosphate buffer solutions pH (7.1 and 3.9) for different times intervals and incubated in a shaking water bath (Lab Tech LSB-015S) at 37±1°C.

The amount of Carbidopa released in the medium was determined by recording the absorbance at 305 nm by using a UV-VIS-PC spectrophotometer (Perkin Elmer Lambda).

2.10 Study of Drug Release Kinetics

Kinetics of drug release (Carbidopa) from PVA-NaAlg IPN hydrogels were tested by using zero order rate, first order rate, Higuchi and Hixon-Crowell drug release kinetic models.

3. RESULTS AND DISCUSSION

3.1 Fourier Transforms Infrared Spectroscopy (FT-IR)

The FT-IR spectra of poly vinyl alcohol showed a broad peak around 3450 cm^{-1} which indicate to the stretching of –OH group, and peaks at 2936 cm^{-1} and 2854 cm^{-1} due to C-H stretching. The FT-IR spectra of sodium alginate showed peaks at 1417 cm^{-1} and 1620 cm^{-1} due to asymmetric and symmetric stretching of carboxylate salt groups. The FT-IR spectra of the PVA-NaAlg IPN hydrogel showed the asymmetrical stretching of $–COO^-$ groups shifted to 1635 cm^{-1}, and the symmetrical stretching shifted to1414 cm^{-1}. The FT-IR results indicate that the PVA-NaAlg IPN hydrogels were formed by using glutaraldehyde as a crosslinked agent.

3.2 Study of Swelling Behavior (Water Uptake)

Due to determine the experimental conditions for optimum loading and releasing of Carbidopa from PVA-NaAlg IPN hydrogels, the swelling behavior of PVA-NaAlg hydrogel was investigated at different times in different phosphate buffer solutions pH (7.1 and 3.9) with incubation at 37°±1.

PVA-NaAlg IPN hydrogel showed a maximum degree of swelling (89.9 W_t. %) at pH(3.9) while showed (76 W_t. %) at pH (7.1) within the first hour of swelling. Degree of swelling of IPN increased to (133.4 W_t. %) at pH (3.9) and (112.5 W_t. %) at pH (7.1) within the first 4 h. After the first 24 h, the degree of swelling increased to (139.5 W_t. %) at pH (3.9) and (118.7 W_t. %) at pH (7.1). Eventually, after 48 h, the maximum swelling was (157.3 W_t. %) at pH (3.9) and (121.6 W_t. %) at pH (7.1).

Figs. 2 and 3 show the swelling behavior of PVA-NaAlg IPN hydrogel in different phosphate buffer solution pH (7.1) and pH (3.9). The study of swelling behavior clearly indicates that PVA-NaAlg IPN hydrogel was suitable for loading and releasing of Carbidopa in phosphate buffer solution pH (3.9).

3.3 Scanning Electron Microscopy (SEM)

The morphology of the cross section and the outer surface of the PVA-NaAlg IPN hydrogel before and after releasing drug (Carbidopa) was investigated by SEM.

The SEM images of the IPN hydrogel Fig. 4 (A, B, C, D) (before releasing drug) show clearly the outer and cross section of surface morphology.

Observing the SEM photographs in Fig. 4 (A and B) indicated that there is blend homogeneity between PVA and NaAlg network. The SEM images also show partially roughness outer surface with some layer-shaped folds. Fig. 4 (C), shows the cross section of the IPN hydrogel which has the undulant and tight surface with some folds and cohesive composite. At higher magnification, Fig. 4 (D) shows that the cross section contains folds in the polymeric structure. Thus, they are useful for more water swelling.

However, Fig. 5 (A, B, C, D) shows the SEM images of IPN hydrogel after releasing drug. Fig. 5 (A) specifically, shows the composite morphology of the outer surface with different types of cracks distributed over the whole surface which proves that degradation was started deeply and in all directions as a result to some depletion of PVA and NaAlg from IPN hydrogel and then releasing the drug, which is supported by the fact that 61%Wt degradation

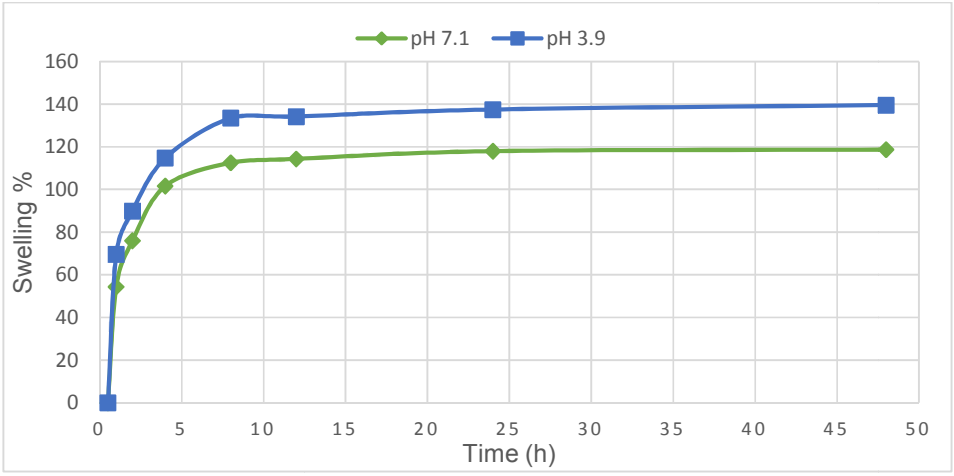


Fig. 2. Swelling behavior of PVA-NaAlg IPN hydrogel in different phosphate buffer solution pH (3.9 and 7.1)

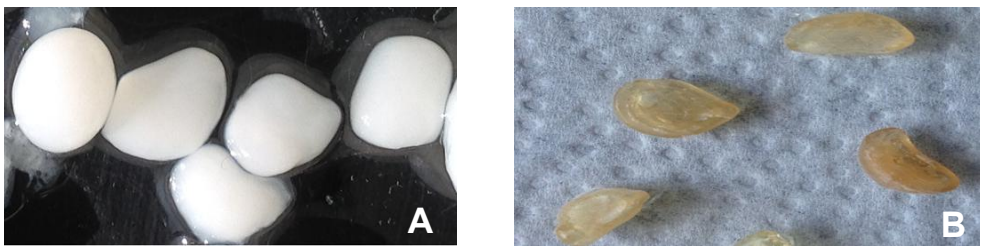


Fig. 3. PVA-NaAlg IPN hydrogel (A) after swelling (B) before swelling

IPN hydrogel was happened after 23 days. Fig. 5 (B) shows clearly the layer-shaped folds after releasing drug, which refers to the mechanism of Carbidopa releasing concerning both diffusion and erosion mechanisms. Fig. 5 (C) shows the surface morphology between layer-shaped folds and clearly coarse surface. At higher magnification, Fig. 5 (D) shows inner composite of the layer-shaped of IPN hydrogel after releasing, which was similar to the 3D composition.

3.4 Study of Drug Releasing

The release of Carbidopa from PVA-NaAlg IPN hydrogel was investigated at 37°C±1 in different phosphate buffer solutions pH (7.1 and 3.9).

Fig. 6 shows the percentage release curve of Carbidopa. It can be seen that the drug released from PVA-NaAlg IPN was (73.9%) at pH (7.1) and (85.8%) at pH (3.9) within 24 h.

This suggests that the drug release properties of PVA-NaAlg IPN hydrogel were pH sensitive.

Table 1. Targeted and actual drug loading in PVA-NaAlg IPN hydrogel in different phosphate buffer solutions

pH medium	Targeted drug loading %	Actual drug loading%	Drug loading efficiency
7.1	5	3.6	73
3.9	5	4.2	85

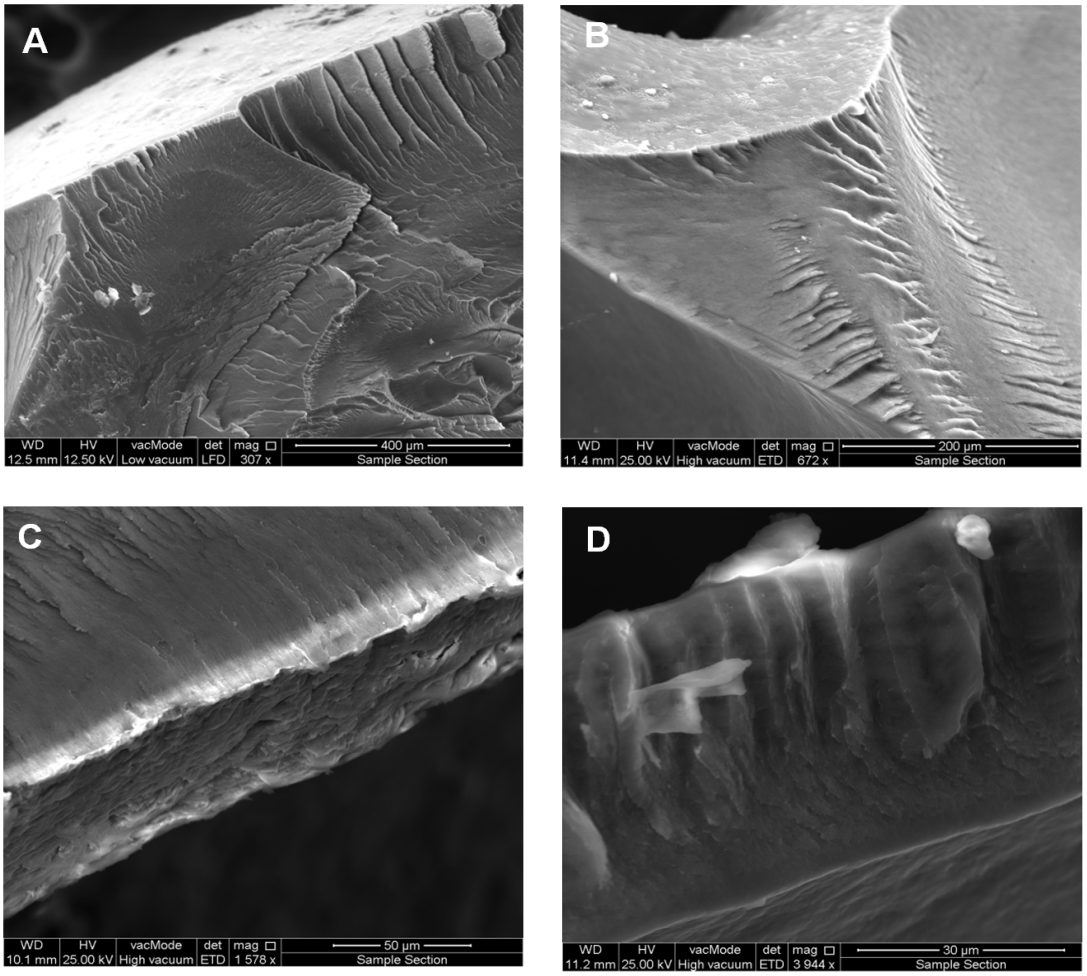


Fig. 4. SEM of PVA-NaAlg IPN hydrogel (A,B,C,D) before releasing drug

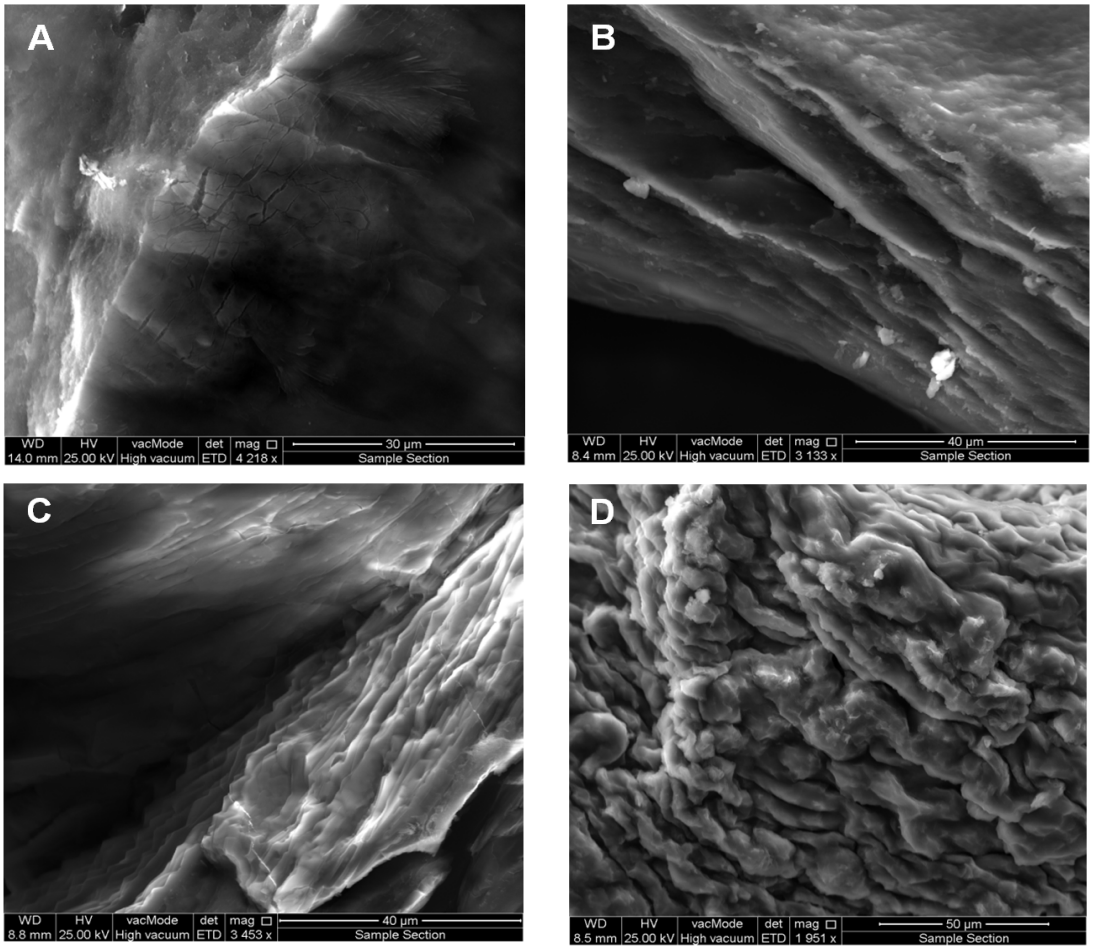


Fig. 5. SEM of PVA-NaAlg IPN hydrogel (A,B,C,D) after releasing drug

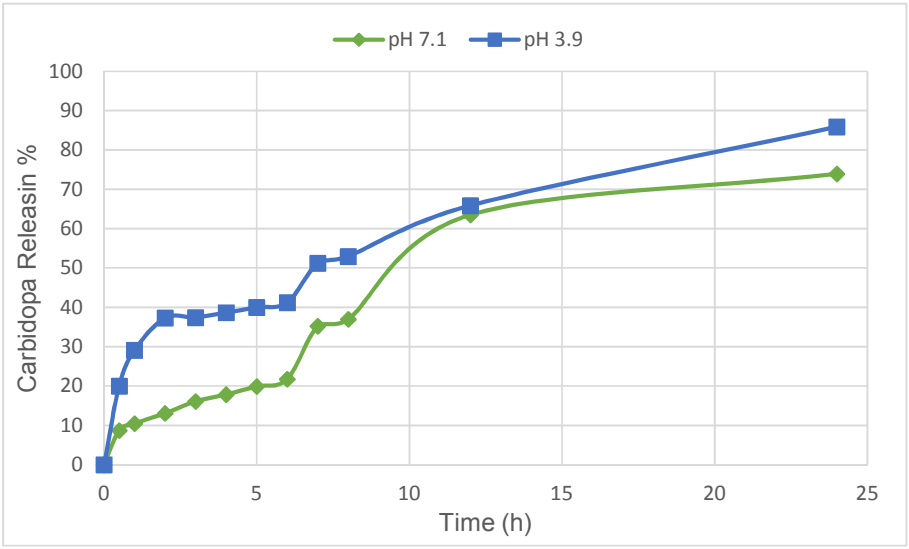


Fig. 6. Carbidopa releasing from PVA-NaAlg IPN hydrogel in different phosphate buffer solutions pH (3.9 and 7.1)

Clearly, it has been observed that the total (10.4%) of drug release occurred within 1 h at pH (7.1) whereas at pH (3.9) the total was (29%) drug release. After 3 h, the release pattern showed that at pH (3.9), the total drug release increased to (37.4%), but increased to (16%) at pH (7.1). After 12 h, the release pattern showed that at pH (3.9) the total drug release increased to (65.8%), whereas it increased to (63.4%) at pH (7.1).

Therefore, the results suggest that the amount of Carbidopa release at pH (3.9) was higher than release medium of pH (7.1). This can be related to the swelling behavior of the IPN (Fig. 2). The swelling was increasing when pH of the medium changed from neutral to acidic.

3.5 The Kinetic of Drug Release from PVA-NaAlg IPN Hydrogel

Seeking 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.

Hixson-Crowell model: $W_0^{1/3} - W_t^{1/3} = \kappa t$

Where W_0 is the initial amount of drug in the buffer solution, Wt is the remaining amount of drug in the buffer solution at time t, and κ (kappa) is a constant incorporating the surface-volume relation.

When the obtained dissolution data were fitted into the zero-order kinetic model, it was evident (Figs. 7 and 8 and Table 2) that the plots were curvilinear for all formulation (different phosphate buffer solutions pH 3.9 and 7.1). The small regression values, suggest that the release kinetic did not follow the zero-order.

On the other hand, the obtained dissolution results were found to fit well the first-order kinetic model. It is clearly evident from Figs. 7 and 8 as well as regression parameters illustrated in Table 2 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 (0.7047 at pH 3.9 and 0.8764 at pH 7.1) were higher than those obtained for zero-order kinetic equation (0.6554 at pH 3.9 and 0.852 at pH 7.1). These data suggest strongly a diffusion Carbidopa release mechanism from PVA-NaAlg IPN hydrogel.

Beside the first-order mechanism model, the mechanism of drug releasing from PVA-NaAlg IPN hydrogel was evaluated by fitting the dissolution data of the drug releasing profiles to Higuchi's square root model equation of diffusion. It can be observed from Figs. 7 and 8 as well as Table 2 that a linear relationship was obtained with all the formulations (different phosphate buffer solutions pH 3.9 and 7.1) (0.8862 at pH 3.9 and 0.9834 at pH 7.1) which indicated that the release of Carbidopa from PVA-NaAlg IPN hydrogel was done by the diffusion mechanism.

Furthermore, to determine whether the erosion was also involved in the drug releasing from PVA-NaAlg IPN hydrogel, the dissolution data of drug release profile were fitted to Hixson-Crowell cube root law. The r^2 values were (0.6884 at pH 3.9 and 0.8679 at pH 7.1) indicating that the relationship was semi-linear for all formulations (different phosphate buffer solutions pH 3.9 and 7.1). This implies that an erosion might have also occurred in the release of drug from PVA-NaAlg IPN hydrogel. So, the release of Carbidopa from PVA-NaAlg IPN hydrogel may be attributed to both diffusion and erosion mechanisms. Diffusion might be dominating the release in the initial hours.

Table 2. Kinetics data of Carbidopa release from PVA-NaAlg IPN hydrogel in different phosphate buffer solutions pH (3.9 and 7.1)

pH medium	Zero-order		First-order		Higuchi's		Hixson-Crowell	
	r^2	K_0	r^2	K_0	r^2	K_0	r^2	K_0
3.9	0.6554	14.921	0.7047	1.9259	0.8862	6.2122	0.6884	0.2526
7.1	0.852	4.9315	0.8764	1.9781	0.9834	1.2658	0.8679	0.0776

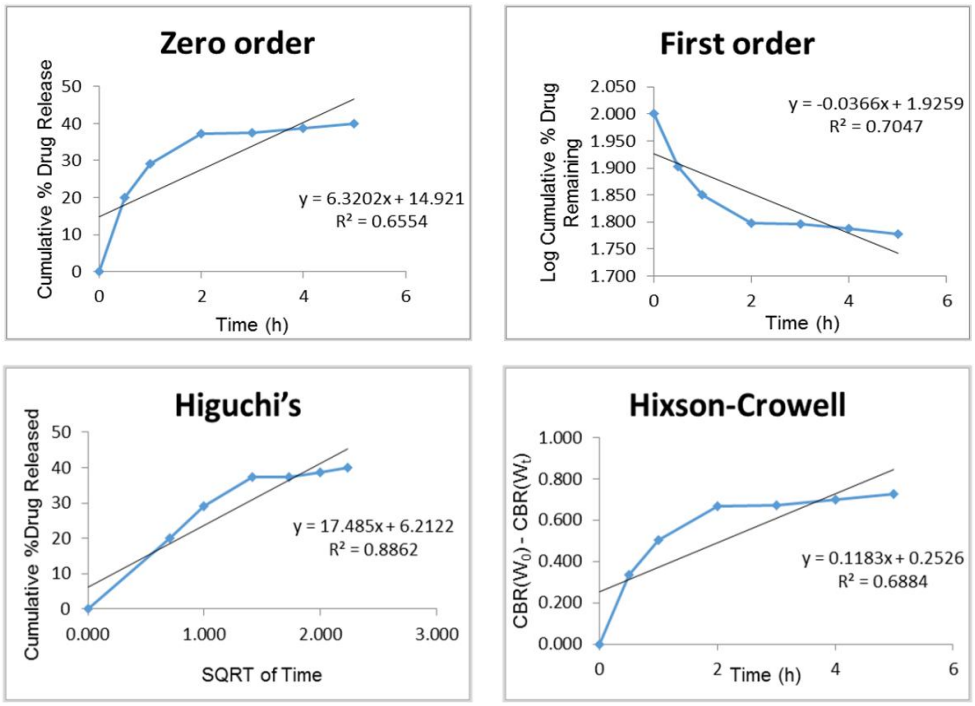


Fig. 7. Comparative plots of *in vitro* release profile, Zero order release kinetic, First order release kinetic, Higuchi's (SQRT) release kinetic and Hixson-Crowell kinetic model in phosphate buffer solution at pH 3.9

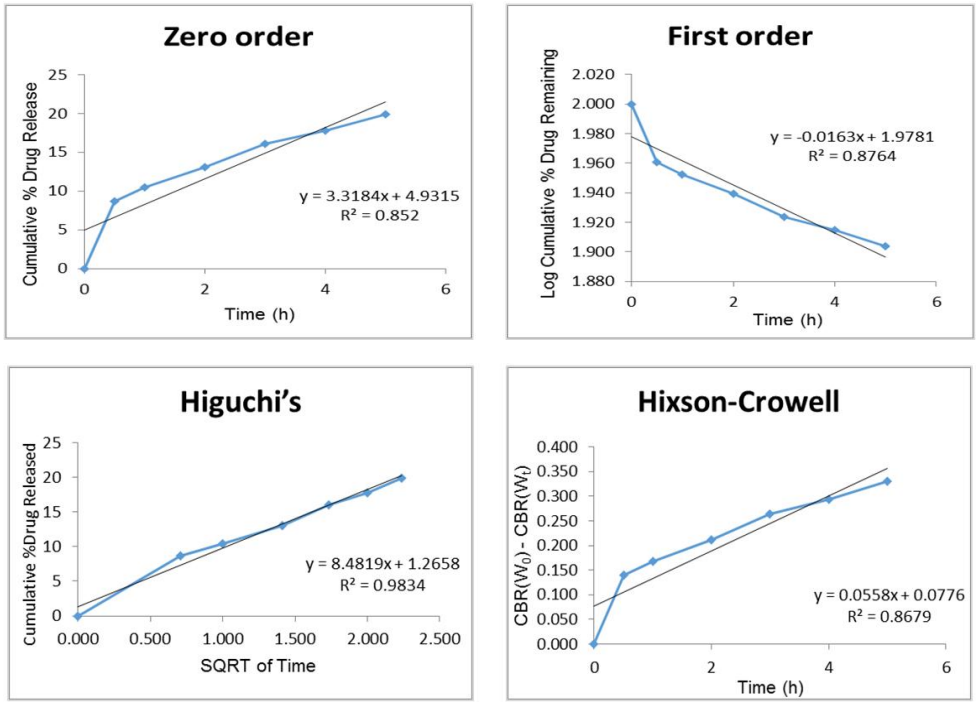


Fig. 8. Comparative plots of *in vitro* release profile, Zero order release kinetic, First order release kinetic, Higuchi's (SQRT) release kinetic and Hixson-Crowell kinetic model in phosphate buffer solution at pH 7.1

4. CONCLUSIONS

PVA-NaAlg IPN hydrogels for controlled delivery of Carbidopa were prepared by using glutaraldehyde as a crosslinked agent between poly vinyl alcohol and sodium alginate. The prepared IPN hydrogels were characterized by studying swelling behavior (where swelling at pH 3.9 was better than pH 7.1), FT-IR spectroscopy(–COO^- groups shifted from 1620 cm^{-1} to 1635 cm^{-1} for asymmetrical stretching and the symmetrical stretching shifted from 1417 cm^{-1} to1414 cm^{-1}. This proves that PVA-NaAlg IPN hydrogels) was formed. The surface morphology (SEM) shows the outer and cross-section surface of hydrogel before releasing drug and shows the degradation after releasing drug. The hydrogels showed 61%Wt degradation within 23 days. The loading and releasing characteristics of IPN hydrogels were evaluated. The models of kinetics of releasing drug were studied by using different types of mechanisms (Zero-order, First order, Higuchi's model and Hixson-Crowell model), the release of Carbidopa from hydrogel may be attributed to both diffusion and erosion mechanisms. The PVA-NaAlg IPN hydrogels were nontoxic and biodegradable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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