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Sodium Alginate - Gelatin Cross-Linked Microspheres for Releasing Diltiazem Hcl

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Abstract:

Semi-interpenetrating polymer network (semi-IPN) microspheres of Sodium alginate (NaAlg) and Gelatin were prepared and cross-linked with glutaraldehyde by using emulsification/solvent-evaporation method to deliver Diltiazem HCl as a model of drug. Diltiazem HCl was successfully loaded into NaAlg-Gelatin microspheres in different ratios of NaAlg and Gelatin. The prepared microspheres were characterized by Fourier Transmission Infrared Microscopy (FT-IR) and Scanning Electron Microscope (SEM). The effects of different process parameters, like percentage of polymers, swelling behavior and in vitro drug release of microspheres in different phosphate buffer solutions pH (7.1and3.9) 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: *drug delivery system, sodium alginate, gelatin, Semi-interpenetrating polymer network microspheres.*

Introduction:

Hydrogels are unique class macromolecular network that can hold a large fraction of an aqueous solvent within their structures. Specifically they are useful for biomedical applications, specially controlled drug delivery because of their ability to simulate biological tissues (Peppas NA. et al. 2006, Huang X. et al. 2001). Controlled release technology contributes importantly in the fields of medicine, pharmacy and agriculture (Lavan D. A. et al. 2003). So, it is very clear that in these areas, natural polymeric materials have been preferred over synthetic polymers for their low cost, non-toxicity, availability and biodegradability properties (Pepperman A. B. et al. 1995, Kumbar S. G. et al. 2002).

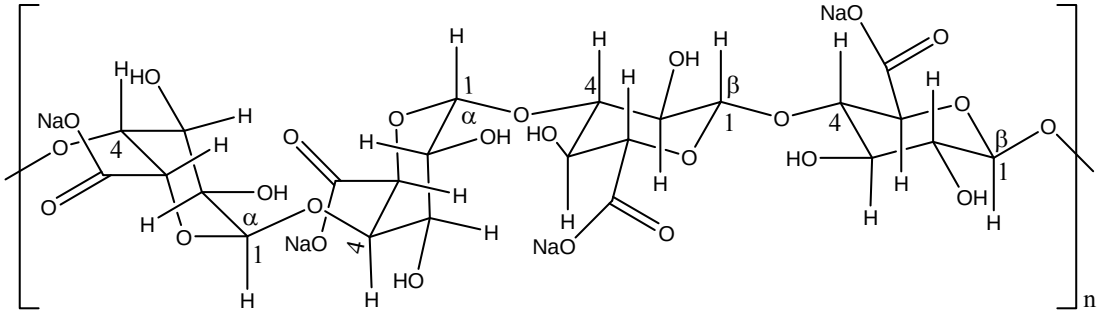


Figure (1): Structure of Sodium alginate

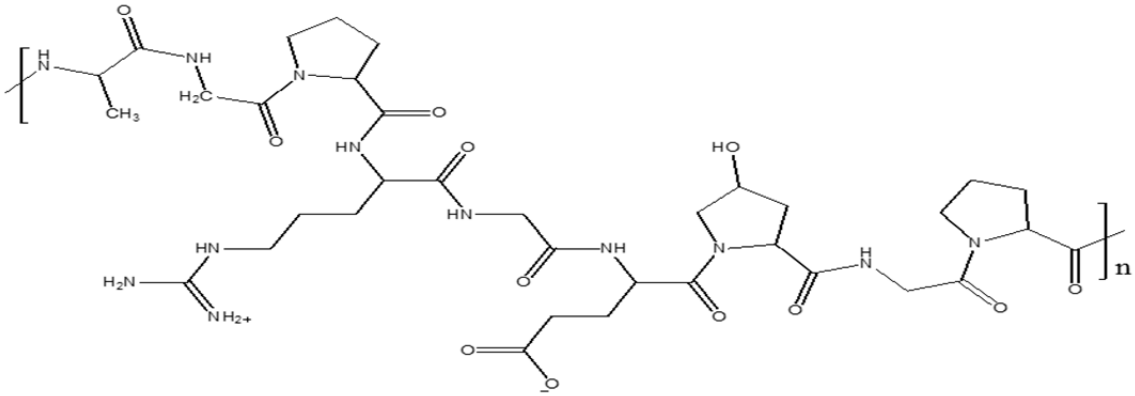


Figure (2): Structure of Gelatin

Biodegradable polymers derived from sodium alginate and gelatin have cleared that they are very suitable pharmaceutical industries due to their good ability drug releasing (Kulkarni A. R. et al. 2000, Fang Y-E. et al. 1998, Pourjavadi A. et al. 2007). Sodium alginate (see

Fig. 1) has been listed as a safe substance by the Food and Drug Administration (FDA) (Simpson NE. et al. 2004). In production, sodium alginate can be extracted from brown alga and it is sodium salt of alginic acid with a high viscosity. So, it is often used as an emulsifier and gelling agent. Such properties enable sodium alginate to be used widely in drug delivery system (Fan L. et al. 2005).

Gelatin is obtained by the thermal denaturation of collagen from animal skin, bones and fish scales. It contain mainly the residue of 3, 4-hydroxyproline in its structure in Fig. (2) (Oakenfull D. et al. 2003, Babin H. et al. 2001). Diltiazem HCL represents calcium channel blocker (Tapia C. et al 2005) and used as a cure for hypertension and angina (Tripathi K. D. 2003). Diltiazem HCl (see Fig. 3) was selected as model drug for investigation because of its suitable properties such as half-life of 4.5 h, optimum partition coefficient (158) and molecular weight (450.98 g/mol). All the properties make it suitable for administration by buccal route. A suitable buccal drug delivery system requires good bio adhesive properties. They, it stays in oral cavity for desired duration, localize the dosage from specific region, and control the release rate of drug (Gaur R. et al. 2009).

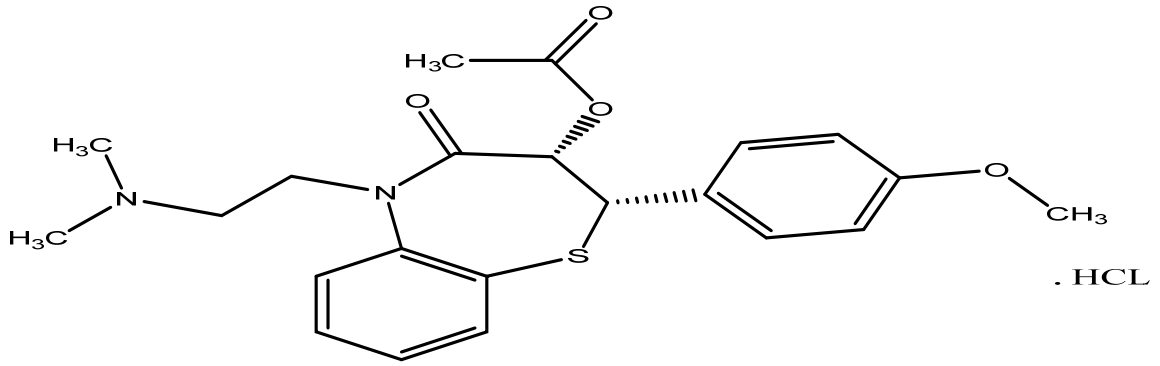


Figure (3): Structure of Diltizamen HCL.

In this study, Sodium alginate-gelatin (NaAlg-Gelatin) microspheres were prepared by using glutaraldehyde as a crosslinked and choosing Diltiazem HCL as a drug model. Properties of hydrogel microspheres such as swelling behavior, FT-IR, morphology (SEM) and size distribution were investigated. In addition, loading and releasing s of Diltiazem HCL from the microspheres were investigated too. According to our literature survey, there is no report available about the formation of (NaAlg-Gelatin) microspheres for the controlled release of Diltiazem HCL.

EXPERIMENTAL

Materials

Sodium alginate (medium viscosity) was purchased from BDH chemical company, UK. Gelatin was obtained from sigma-Aldrich chemical company, UK. Diltiazem HCL was purchased from Awamedica pharmaceutical company, Erbil Iraq. Glutaraldehyde was supplied by India institute of Technology, ROORKE, India. All other chemical were used without any further purification.

Preparation of NaAlg-Gelatin (Semi-IPN) microspheres

The NaAlg-Gelatin Semi-IPN microspheres were prepared by using various concentrations of NaAlg (for details see Table1). NaAlag solutions were prepared by dissolving NaAlg in distilled water at room temperature with stirring (200 rpm) until a homogenous solution was obtained. The gelatin was dissolved in distilled water at (40-50 ^{o}C) with stirring (200 rpm) until homogenous solution was appeared. Both polymer solutions were carefully mixed at various ratios.

The required amount of glutaraldehyde and (100 µml) of HCL conc. was added with stirring (200 rpm) until microspheres were obtained. The microspheres formed were filtrated, washed with hot water and cold water and vacuum dried at (35 ^{o}C).

Table (1): Composition of the Sodium alginate-Gelatin (Semi-IPN) microspheres

No. of sample	NaAlg-Gelatin ratio	GA(µml)	Water (ml)
1	80:20	200	25
2	80:40	200	25
3	40:40	200	25
4	40:80	200	25
5	20:80	200	25

Furrier Transmission Infrared Spectroscopy (FTIR)

The FTIR spectrum of the sodium alginate, gelatin, and NaAlg-Gelatin microspheres were done by using a (Perkin Elmer model-spectrum one) type FTIR spectrometer (in the region between 450-4000 cm^{-1}).

Study of Swelling Behavior

In order to measure the swelling (S_w) degree of NaAlg-Gelatin microspheres , (100mg) of the microspheres were kept in (25 ml) of different phosphate buffer solutions (pH 7.1 and pH 3.9) and incubated at 37° C.

The increase in weight (W_t-W_0) of microspheres at different time intervals in comparison to the initial weight (W_0) of microsphere was used to calculate the degree of swelling (S_w) by using equation (1).

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

Where W_0 and W_t are the initial and final weights of microspheres.

Morphological study of (NaAlg-Gelatin) microspheres

The morphology study of NaAlg-Gelatin microspheres 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).

Determination of calibration curve

Calibration curve of Diltiazem HCL was prepared by using different phosphate buffer solutions (pH 7.1 and 3.9) in the concentration range (3-15 mg/ml). The drug concentration was analyzed by using UV-VIS-PC spectrophotometer (Perkin Elmer Lambda) at 237nm.

Determination of percentage drug entrapment

In order to determine the percentage of drug loading (PDL), (100mg) of dry NaAlg-Gelatin microspheres 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 2hr, to ensure the complete extraction of drug from the microspheres. At the end of the 2h, it was filtered to remove debris. They drug was analyzed by using UV-VIS-PC (Perkin Elmer lambda 25) at a wave length 237nm. 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 show in [Table (2)]. The drug loading in hydrogel microspheres was estimated by using equation (2):

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

Where PDL = percentage of drug loading

Loading of Diltiazem HCL in (NaAlg- Gelatin) microspheres

A modified emulsification /solvent – evaporation method (Şanlı O. et al. 2009) was used for loading Diltiazem HCL into NaAlg-Gelatin microspheres. (100 mg) of Diltiazem was dissolved in dichloro methane, then added to the (NaAlg-Gelatin) polymer solution with glutaraldehyde then stirring to form a stable oil/water emulsion system at room temperature. Stirring was continued until microspheres were formed and the dichloro methane was evaporated. Microspheres were filtered, washed with hot and cold water and vacuum dried at 35 °C.

In-Vitro release study

The release characteristic of (NaAlg-Gelation) microspheres were determined by keeping (100 mg) of NaAlg- Gelatin microspheres with loaded Diltiazem HCL in (50 ml) of different phosphate buffer solutions (pH 3.9 and 7.1) for different time intervals and incubated in a shaking water bath(model LSB-

015S LABTECH) at 37 °C. The amount of Diltiazem HCL released in the media was determined by recording the absorbance (ƛ max = 237nm) by a (Perkin Elmer lambda 25) UV-VIS-PC spectrophotometer.

RESULT AND DISCUSSION

Furrier Transmission Infrared Spectroscopy (FTIR)

FTIR spectroscopy, in the spectral region, between 450-4000 cm^{-1} was used to assess the polymer chemical groups (sodium alginate, gelatin and NaAlg-Gelatin microspheres) and investigate the formation of cross-linked network from the blends by using glutaraldehyde.

The FTIR 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 FTIR spectra of gelatin showed peaks at 3434 cm^{-1} due to –N-H stretching of amide, C=O stretching at 1635 cm^{-1} and C-H stretching at 2922 cm^{-1}. The FTIR of NaAlg-Gelatin microspheres showed the asymmetric stretching of –COO- groups shifted to 1630 cm^{-1} and the symmetric groups shifted to 1412 cm^{-1}. The FT-IR results indicate the NaAlg-Gelatin microspheres were formed by glutaraldehyde as across-linked.

Degree of swelling (%Sw) in (NaAlg-Gelatin) microspheres

Due to determine the experimental conditions for optimum loading and releasing of Diltiazem HCl from (NaAlg-Gelatin) microspheres, the swilling behavior of (NaAlg-Gelatin) microspheres was studied at different time intervals in different phosphate buffer solutions (PH 3.9 and 7.1).

Sample 1 of NaAlg-Gelatin microspheres showed a maximum degree of swelling (77.7 Wt %) at pH (3.9), and showed (86.02 Wt %) at pH (7.1) within the first hour, while sample 2 showed (56.6 Wt %), sample 3 (47.6 Wt %), sample 4 (36.9 Wt %) and sample 5 (33.4 Wt %) all at pH 3.9. However, sample 2 showed (48.4 Wt %), sample 3 (37.3 Wt %), sample 4 (32.4Wt %) and sample 5 (30.7 Wt %) at pH (7.1).

Degree of swelling of sample 2 increased to (87.9 Wt %) while sample 3 increased to (82.5 Wt %). Sample 1 showed again a maximum swelling (102.2 Wt %) at pH (3.9). Whereas, sample 2 showed (57.5 Wt %), sample 3 (51.06 Wt %) and sample 1 showed a maximum swelling again (121.3 Wt %) at pH (7.1) within the first four hour. After the first 12 h, the degree of swelling of sample 2 increased to (96.3 Wt %), sample 5 to (68.7 Wt %) at pH (3.9), sample 1 to (142.2 Wt %) showed a maximum degree of swelling at pH (3.9) and (131.6 Wt %) at pH (7.1).

After 48h the degree of swelling of sample 2 was increased to (86.8 Wt %), sample 5 to (72.3 Wt %) at pH (7.1) while sample 2 increased to (120.4 Wt %), sample 5 to (97.8 Wt %) at pH (3.9). Finally, sample 1 showed maximum swelling comparing to other samples (141.1 Wt %) at pH (7.1) while (202.2 Wt %) at pH (3.9). Figure (4), (5) and (6) show the swelling behavior of NaAlg-Gelatin microspheres in different phosphate buffer solution pH (3.9 and 7.1).

The study clearly indicates that sample 1 of NaAlg-Gelatin microspheres were suitable for loading and releasing Diltiazm HCl.

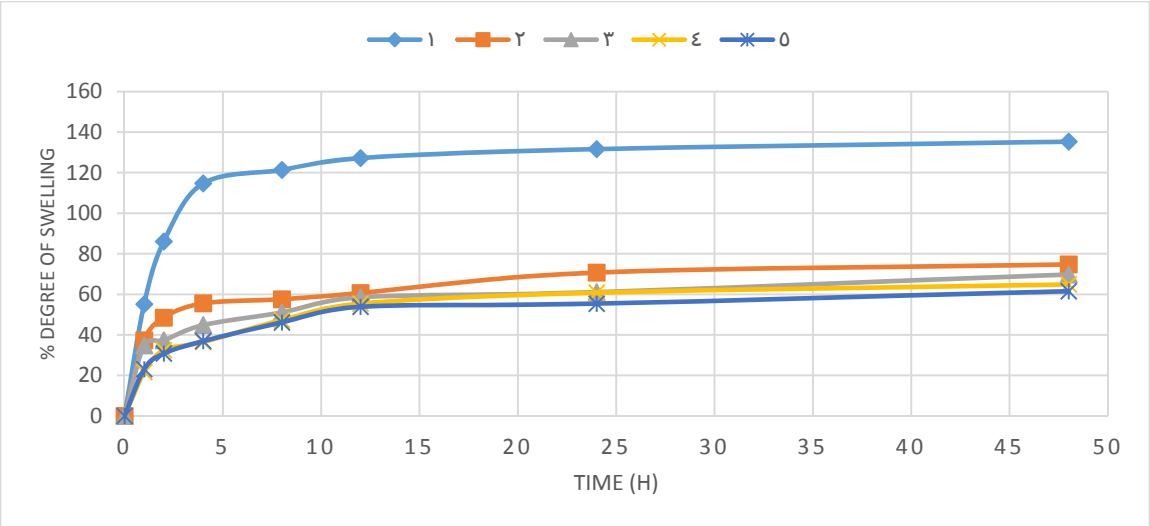


Figure (4): Degree of swelling of NaAlg-Gelatin microspheres in phosphate buffer solution pH 7.1.

Figure (5): Degree of swelling of NaAlg-Gelatin microspheres in phosphate buffer solution pH 3.9.

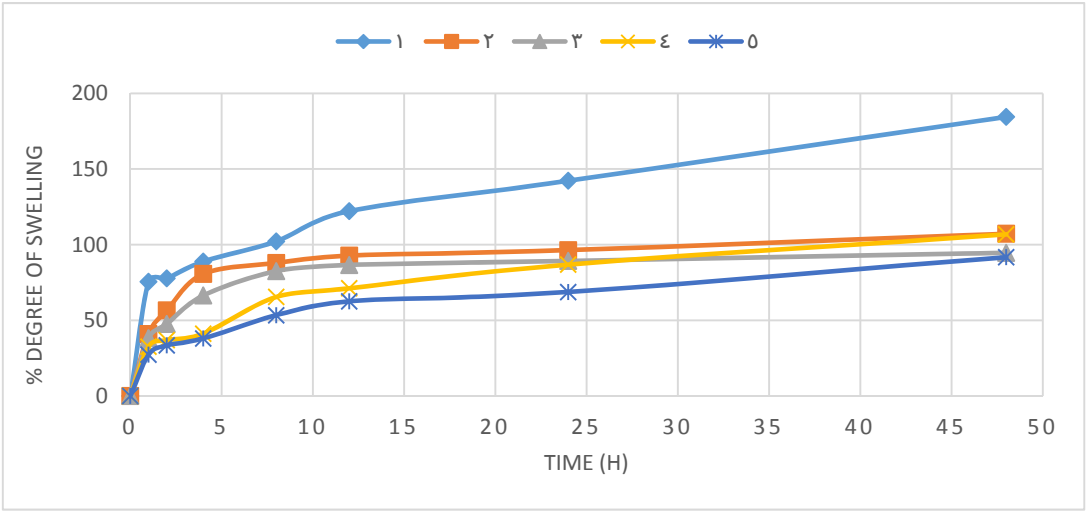


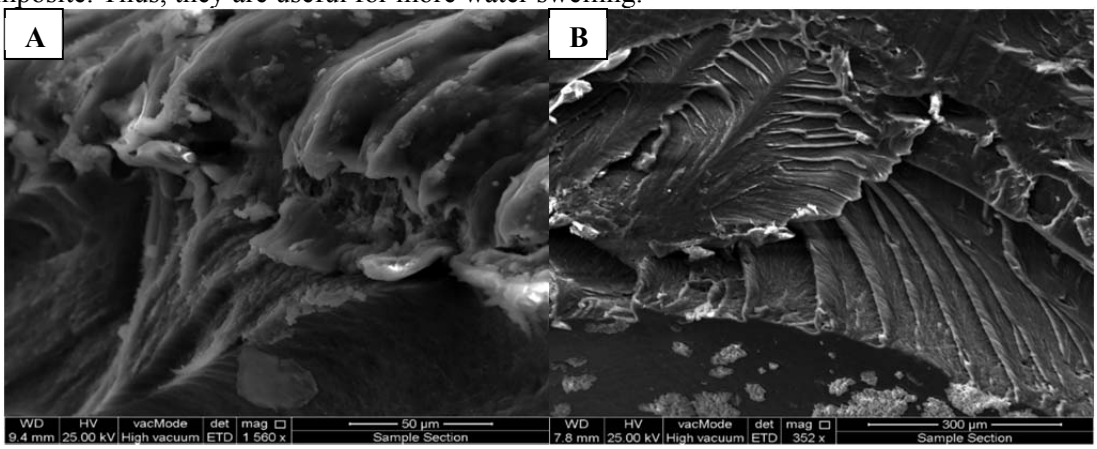
Figure (6): NaAlg-Gelatin microspheres (A) after swelling (B) before swelling.

Scanning Electron Microscopy (SEM)

SEM images and (outer and cross section) surface morphology of NaAlg-Gelatin microspheres samples before and after releasing drug (Diltiazem HCL) were investigated.

The SEM images of the NaAlg-Gelatin microspheres Fig. 7 (A, B, C, D) (before releasing drug) show clearly the outer and cross section surface morphology.

The observation of the SEM imags in Fig. 7 (A, B and C (high magnification)) indicated blend homogeneity between Gelatin and NaAlg network. They show partially roughness outer surface with layer-shaped folds similar a leaf. Fig. 7 (D), the SEM image shows the cross section of the NaAlg-Gelatin microspheres, which appear the undulant and tight surface, with some folds and cohesive composite. Thus, they are useful for more water swelling.



However, Fig. 8 (A, B, C, D) shows the SEM images of NaAlg-Gelatin microspheres after releasing drug. Fig. 8 (A) 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 due to some depletion of Gelatin and NaAlg from microspheres then releasing of drug, which is supported by the fact that 65%Wt degradation of microspheres was happened after 18 days.

Fig. 8 (B) shows clearly the layer-shaped folds after releasing drug, which indicates the releasing mechanism of drug (Dltiazem HCL) because of diffusion. At higher magnification, Fig. 8 (C) shows the surface morphology between layer-shaped folds and clearly coarse surface. Fig. 8 (D) shows inner composite of the layer-shaped folds of microspheres after releasing.

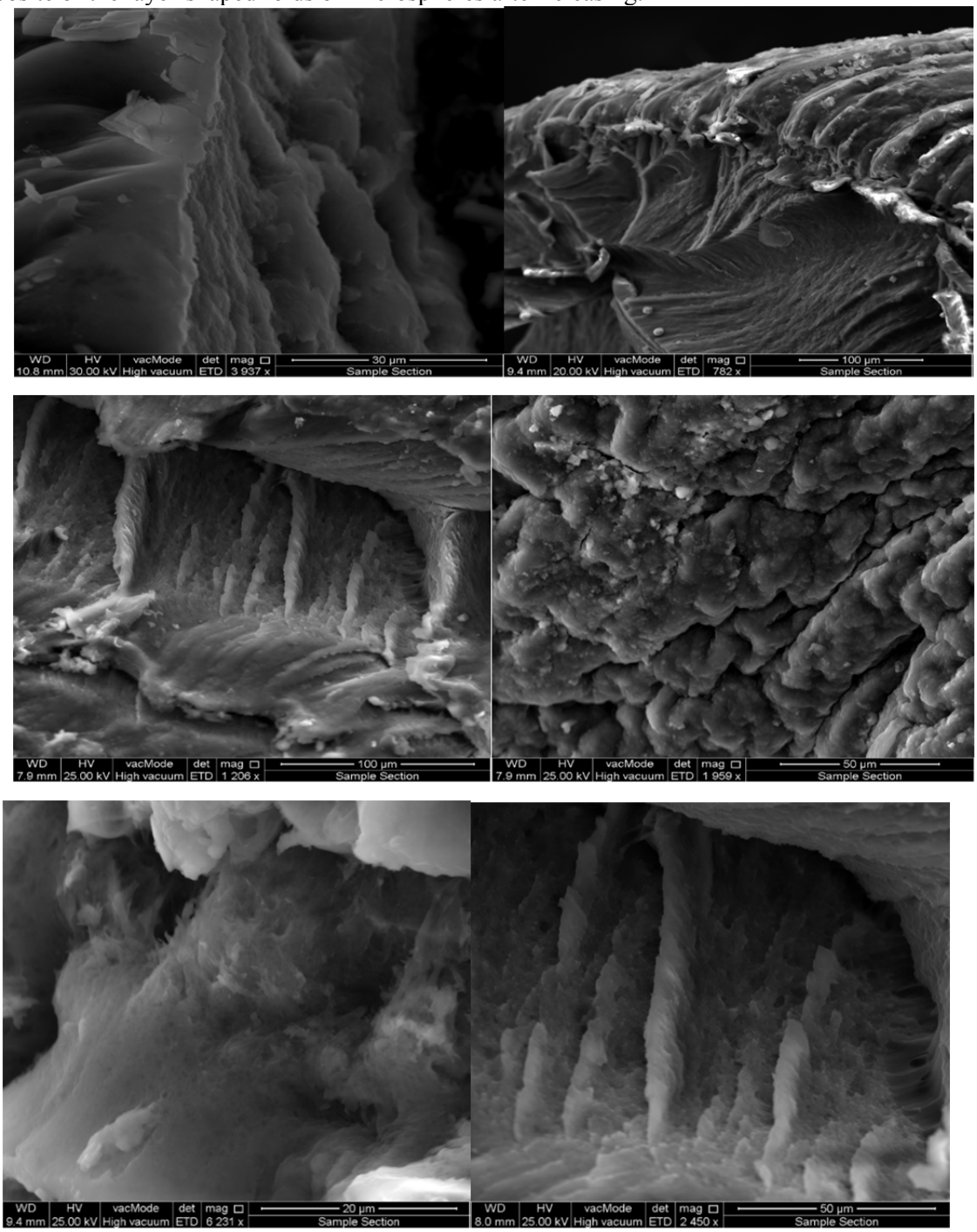


Figure (8): SEM of NaAlg-Gelatin microspheres (A, B, C, D) after releasing drug.

Table (2): Targeted and actual drug loading in NaAlg-Gelatin microspheres in different phosphate buffer solutions.

pH medium	Targeted drug loading %	Actual drug loading%	Drug loading efficiency
7.1	5	3.1	63
3.9	5	4.1	82

Drug release from (NaAlg-Gelatin) microspheres

Figure (9) shows the percentage release curve of Diltiazem HCl from NaAlg-Gelatin microspheres at various pH of medium (7.1 and 3.9) at 37°C in different times. It can be seen that the drug released from NaAlg-Gelatin microspheres was (82.1%) at pH 3.9 and (63.1%) at pH 7.1 within 24h. This suggests that the drug release properties of NaAlg-Gelatin microspheres are pH sensitive.

As shown in Fig. (9), it has been observed that the total (29.4%) of drug release occurred within the first 30 min in pH (3.9), whereas at pH (7.1), the total was (13.6%). After 8h, the release pattern shows that at pH (3.9) the total of drug release increased to (59.7%), whereas it increased to (39.09%) at pH (7.1).

The results suggest that the amount of Diltiazem HCl release at pH (3.9) was higher than release medium of pH (7.1). It can be correlated with swelling behavior of the NaAlg-Gelatin microspheres (Fig 4 and 5), where the swelling was increasing when pH of the medium changed from neutral to acidic.

Figure (9): Diltiazem HCl releasing form NaAlg-Gelatin microspheres in different buffer solutions.

The kinetic of drug release from NaAlg-Gelatin microspheres

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:

$$\log C = \log C0 - Kt/2.303$$

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

Higuchi's model:

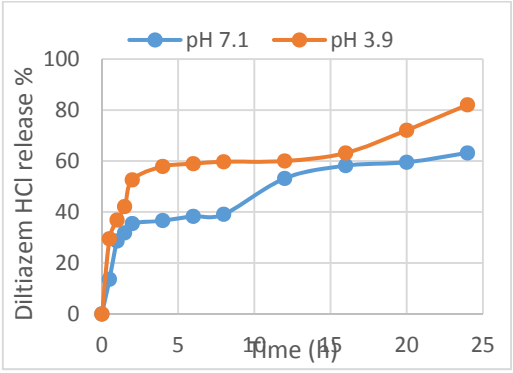
$$Q = KHt1/2$$

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

Hixson-Crowell model:

$$W0\ 1/3 - Wt\ 1/3 = \kappa t$$

Where W_0 is the initial amount of drug in the buffer solution, W_t 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 is evident (from Fig. (10 and 11) 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 fit well with the first-order kinetic model. It is clearly evident from Fig (10 and 11) 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, these ^{r2} values of first-order kinetic equation (0.7333 at pH 3.9 and 0.5876 at pH 7.1) higher than those obtained for zero-

order kinetic equation (0.6275 at pH 3.9 and 0.5453at pH 7.1).

These data suggest strongly a diffusion Ditliazem HCL release mechanism from NaAlg-Gelatin microspheres.

Beside the first-order mechanism model, the mechanism of drug release from NaAlg-Gelatin microspheres was evaluated by fitting the dissolution data of the drug release profiles to Higuchi's square root model equation of diffusion. It can be obsarve from Fig. (10 and 11) as well as Table (3) that a linear relationship was obtained with all the formulation (different phosphate buffer solutions pH 3.9 and 7.1) (0.8859 at pH 3.9 and 0.8133 at pH 7.1) which indicated that the release of Ditliazem HCL from NaAlg-Gelatin microspheres was through the diffusion mechanism.

Furthermore, to determine whether the erosion was also involved in the drug release from NaAlg-Gelatin microspheres, the dissolution data of drug release profile were fitted to Hixson-Crowell cube root law. The r^2 values (0.6995 at pH 3.1 and 0.5732 at pH 7.1) were small, which suggest that the release kinetic did not follow the Hixson-Crowell cube root law. The release of Ditliazem HCL from NaAlg-Gelatin microspheres can be attributed to diffusion mechanism (Higuchi's square root model).

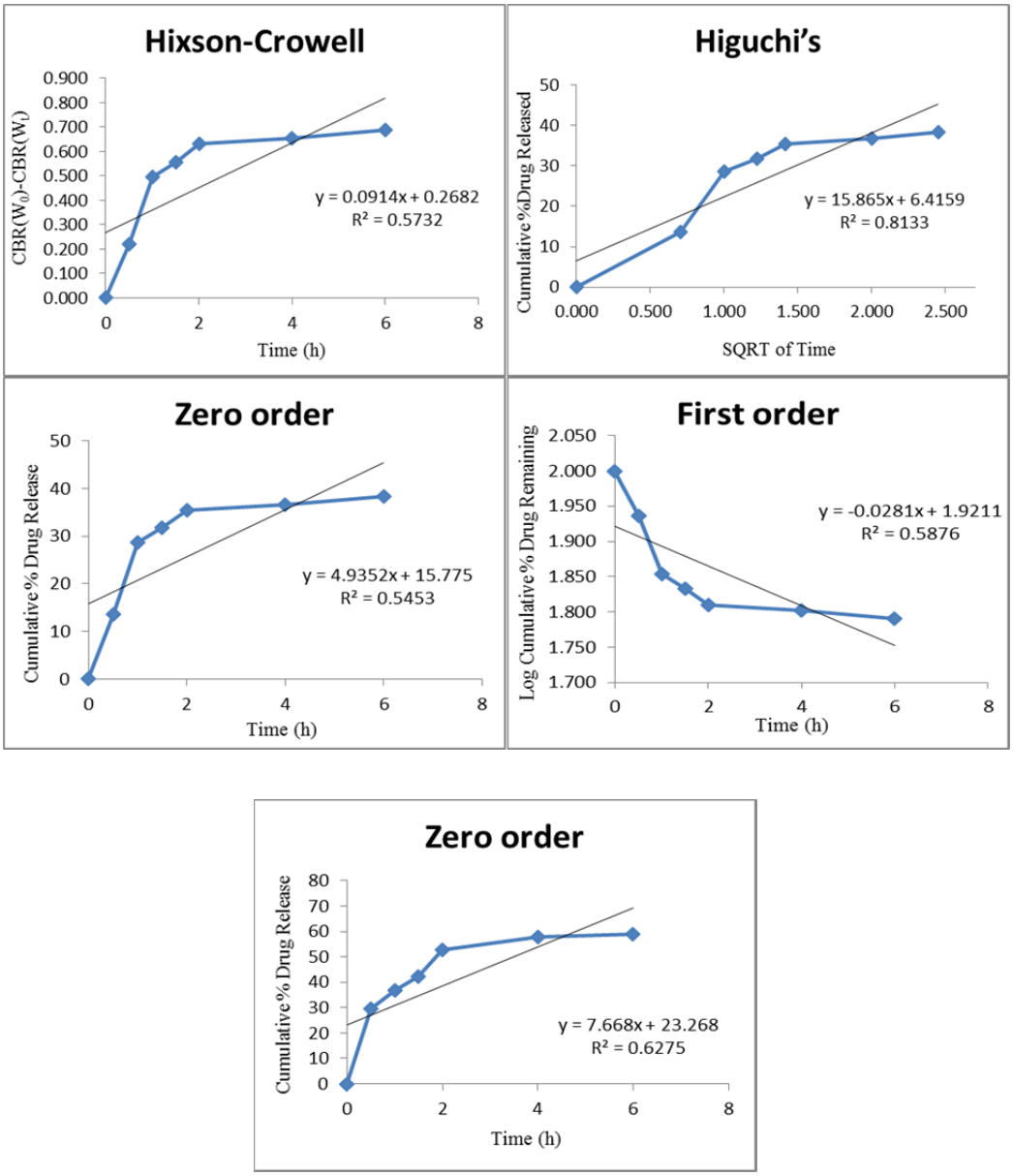


Figure (10): Comparative plots of in vitro release profile, Zero order release kinetic, First order release kinetic, Higuchi's (SQRT) release kinetic and Hixson-Crowell kinetic model in phosphate buffer solution at pH 7.1.

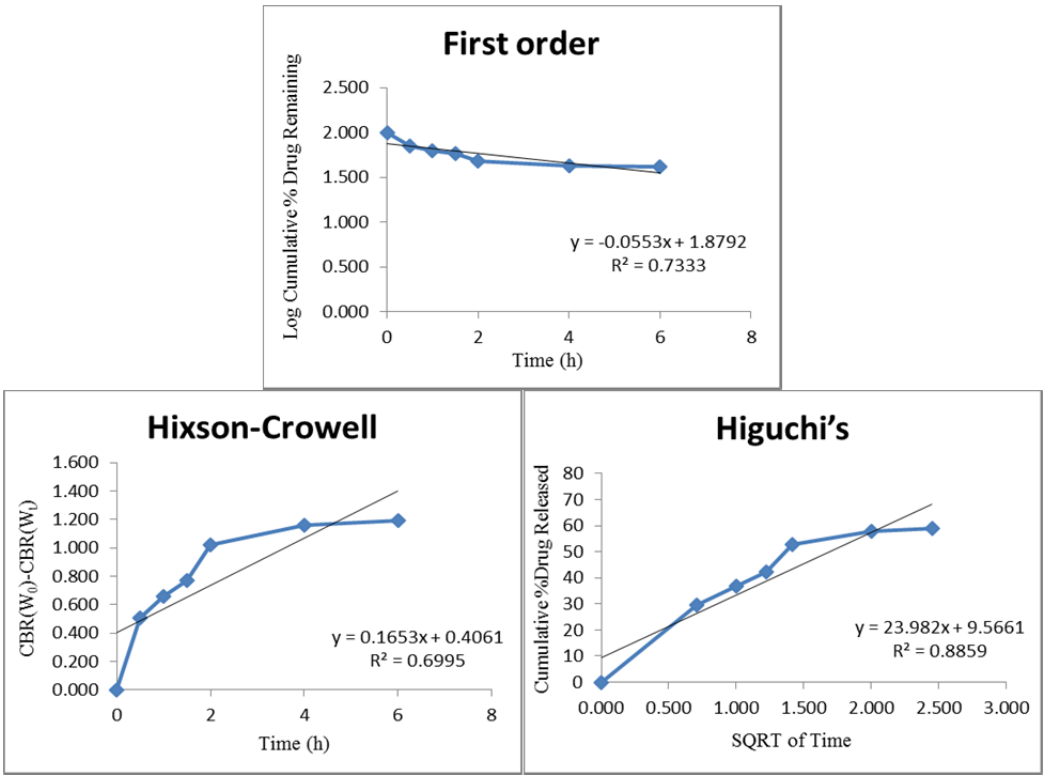


Figure (11): Comparative plots of in vitro release profile, Zero order release kinetic, First order release kinetic, Higuchi's (SQRT) release kinetic and Hixson-Crowell kinetic model in phosphate buffer solution at pH 3.9.

Table (3): Kinetics data of Diltiazem HCl release from NaAlg-Gelatin microspheres 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	0.6275	23.268	0.7333	1.8792	0.8859	9.5661	0.6995	0.4061
7.1	0.5453	15.775	0.5876	1.9211	0.8133	6.1459	0.5732	0.2682

Conclusions

The analysis of swelling ,FTIR, SEM, loading and releasing trends of Diltiazem HCL from NaAlg-Gelatin microspheres with different percentages of NaAlg and Gelatin in different phosphate buffer solutions clearly indicate that the pH solutions and sodium alginate amount play a significant role in controlling Diltiazem HCL release characteristics from microspheres.

The (80:20) (NaAlg-Gelatin) microspheres prepared were more efficient in controlled release of Diltiazem HCL than other percentage of (NaAlg-Gelatin) microspheres and showed (65 W_t. %) degradation within 18 days. The cross-linked microspheres by glutaraldehyde studied were non- toxic and biodegradable.

Acknowledgement

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کورتیا لێکولینێ:

ئامانج لەم لیکۆلینەوە ئەوەیە بۆ بەکارهینانی ریگایکی پیشکەوتو بۆ ئامادە کردنی (Semi-Interpenetration Polymer Network (semi-IPN))بەبەکارهینانی پۆلیمەری (جیلاتین لەگەل سۆدیومی الجینیت) کە (دیلتازم هیدروکلورایدە) تیادا وەك مادەیەکی دەرمانی هەلبژیردراو (ئەم ریگایە بەسەرکەوتوی پەسەند کرا) دواتر بەبەکارهینانی ریگایی شیراو لەسەر هەلی توینەر وە بەکارهینانی (الکلوتر الدیهاید) وەك کارای هاوبەش. دەستنیشان کرا (microspheres) بە شەبەنگی تیشکی ژیر سوور وەخویندنی پیکهاتەی سەروو بەبەکارهینانی ووردبینی ئەلیکترونی .

هەرئەوها خویندنەوە کرا بۆ رەوشی هەلچوون وکاریگەی ریژەی پۆلیمەرە بەکارهاتوەکان وە خیرای دەرجونی دەرمان لە دەرەوەی لەشی زیندوو. لەئەنجامەدا وادەرکەوت ریژەی هەلچون زیاد دەکات بە زیاد بوونی بریك(سودیۆمی الجینیت). وهەر ئەوها لیکۆلینەوە لەسەر خیرای دەرجوون3.9 بە بەهای جیاواز لە توانی هایدروجینی(PH)ئەنجام وا دەرکەوت کە بە خیرایC°37 لە (7.1 و3.9) لە توانی هایدروجینی هەر ئەوها وا بوم دەرکەوت لە توانی هایدروجینی کە باشترینە بو لیدانی دەرمان لە (microspheres) کە پیك دیت لە (Zero-order, First order, Higuchi's model and Hixson-Crowell model).

الملخص:

تهدف هذه الدراسة إلى استخدام طريقة مطوره في تحضير الهلاميات الكروية (Semi-Interpenetrating Polymer Network (Semi-IPN)) ذات الإطلاق المسيطر عليه باستخدام البوليمرات (الجيلاتين وصوديوم الجينيت) والتي تحتوي ديلتيازم هيدروكلورايد كماده دوائية مختارة (تم تحميلها بنجاح)، باستخدام طريقة المستحلب/ تبخير المذيب واستخدام الكلوترالديهايد كعامل تشابك. تم تشخيص (Semi-IPN) بمطيافية الأشعة تحت الحمراء ودراسة تركيبة السطح باستخدام المجهر الإلكتروني. وقد تم دراسة سلوك الانتفاخ وتأثير نسبة البوليمرات المستخدمة وسرعة إطلاق الدواء خارج الجسم الحي، فأظهرت النتائج ان نسبة الانتفاخ تزداد بزيادة كمية الصوديوم الجينت الموجودة. كما وتم دراسة سرعة الإطلاق بقيم مختلفة من الأس الهيدروجيني (3.9 و7.1) في 37 م° فأظهرت النتائج إن سرعة إطلاق الدواء في الأس الهيدروجيني (3.9) أفضل من الأس الهيدروجيني (7.1). كما وتم دراسة ميكانيكية إطلاق الدواء من (Semi-IPN) وتتضمن (Zero-order, First order, Higuchi's model and Hixson-Crowell model).