Preparation of Polyelectrolyte Hydrogels and Study Their Controlled Release of Gabapentin

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Abstract

The semi interpenetrating network hydrogels (Z1-Z15) were prepared from different ratio of sodium alginate and linear poly (acrylamide-co-diallyl dimethyl ammonium chloride) then they mixed with the acrylamide and bisacrylamide as cross linking agent and polymerized via redox polymerization to form the semi-IPNs. All prepared semi-IPNs were loaded with three different amounts from Gabapentin as drug model. The swelling characteristics were studied for all semi- IPN hydrogels by determining the swelling ratio (Q).The release of Gabapentin was followed by using U.V. spectroscopy at (202 , 201 and 204) nm at constant temperature (37ºC) in distilled water , simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) respectly. The results of Gabapentin released indicated that all semi-IPNs have the ability to release drug to environment and the amount of Gabapentin released about 50% during two hours. Higuchi equation was used to determine the Higuchi constant which is very useful to forecasting the amount of Gabapentin released theoretically.

Keywords: Polyelectrolyte; Polymer Drug Delivery; Gabapentin

Abbreviations: SGF: Simulated Gastric Fluid; SIF: Simulated Intestinal Fluid; TDDSs: Targets Drug Delivery Systems; CDDSs: Controlled Drug Delivery Systems; SGF: Systems In Simulated Stomach Fluid; SIF: The Simulated Intestinal Fluid; WU: Water Uptake

Introduction

It is rare to use drugs as pure chemicals alone, it is given as the formula of drug structures such as drug delivery systems. Simple solutions can be developed to form these systems through the use of appropriate additives or excipients to prepare the pharmacological structures. The effectiveness of many of drugs is often designed to working at the site of the therapeutic act, So the method of delivery of medication can have a significant impact on its effectiveness. In many cases conventional medications reach the target location in a small amount while the most amount of the medication is distributed in the whole of the body according to its physicochemical and biochemical properties, so it has developed drug delivery systems that improve the drug's pharmacologic action, reduce side effects and toxicity within the body of the organism [1,2]. The transition from simple tablets to tablets of continuous release and the discovery of sophisticated programmable delivery systems led to the delivery of drugs to the target and cells are more accurate [3].

The synergy between chemists, biologists, doctors and biomedical engineers over the past 20 years has led to the development of controlled release technology and has been the best solution for drug delivery systems. It is a type of drug products that is controlled for long periods of time with maintaining drug concentration in the blood Within optimal treatment limits [4,5]. It is justified to resort to these systems instead of traditional medication formulas due to the problems in metabolism or absorption of medication when using traditional systems or to improve the treatment itself and the release of the drug must be in the right part of the body and the rates required for treatment [6,7]. Controlled drug delivery systems are designed to deliver drugs at

controlled rates for specified periods of time and release them at required rates in places where treatment is needed. The concept of drug delivery systems can be classified into two categories:

i. Targeting is one of the controlled release systems and works on delivery of the active ingredient only to the required tissue or organs called Targets Drug Delivery Systems (TDDSs). Examples of such systems include the delivery of chemotherapeutic drugs to tumour sites directly without damage to other healthy tissues [8].

ii. The systems that control the rate and speed of release of the active substance are known as Controlled Drug Delivery Systems (CDDSs) [9].

Polymers are the most materials which widely used in controlled release systems because their manufacturing processes are easy and widely used to design drug release systems as well as easy control of their physical and chemical properties during preparation [10,11]. There are several types of controlled release formulations [12], the first type is long-range release system(sustained release), It provides effective concentrations for long periods of time and reduces the repetition of taking doses to improve therapeutic compliance and reduce the need for repeated visits to clinics [13,14]. The second is Prolonged release system; this system reduces the release of the active ingredient, resulting in a reduction in the toxic effects of this substance and maintenance of the therapeutic activity required for it [15,16].The third is Delayed release; This system delays the release and then release of the active substance without hindrance, for example oral capsules that remain in the stomach intact and break down only at the highest acidic function in the small intestine or colon [17]. The fourth is Repeat action dosage forms; this system is designed to release one dose of medication and for a certain period of time the other dose is released and thus [16,18].

This work consist of preparation of a number of new electrolytic gels polymeric compositions adopted in the composition of the presence of (Acryl Amide, Sodium alginate, linear copolymer (Acryl Amide –co–diallyl dimethyl lammonium chloride) as semi interpenetrating polymer network (semi-IPN) with different weight ratio and loading these semi-IPNs with Gabapentin as a pharmacological drug because of its important pharmacological effects to treat cases of epilepsy and neuropathy and finally study the Gabapentin released from the polymer systems in simulated stomach fluid (SGF), the simulated intestinal fluid (SIF)and distilled water.

Experiments

Materials

Chemicals used in this study were supplied from different sources; Gabapentin was supplied from Zhejiang chiral Medicine chemicals Co. Ltd., China, Poly (acrylamide–co–diallyl dimethyl ammonium chloride) solution 10%wt/v), Sodium alginate, N,N\-Methylene bisacrylamide were supplied from Sigma Aldrich, N,N,N\,N\-Tetramethylene ethylene diamine was supplied from Fluka , Acryl amide was supplied from Merck Co. .
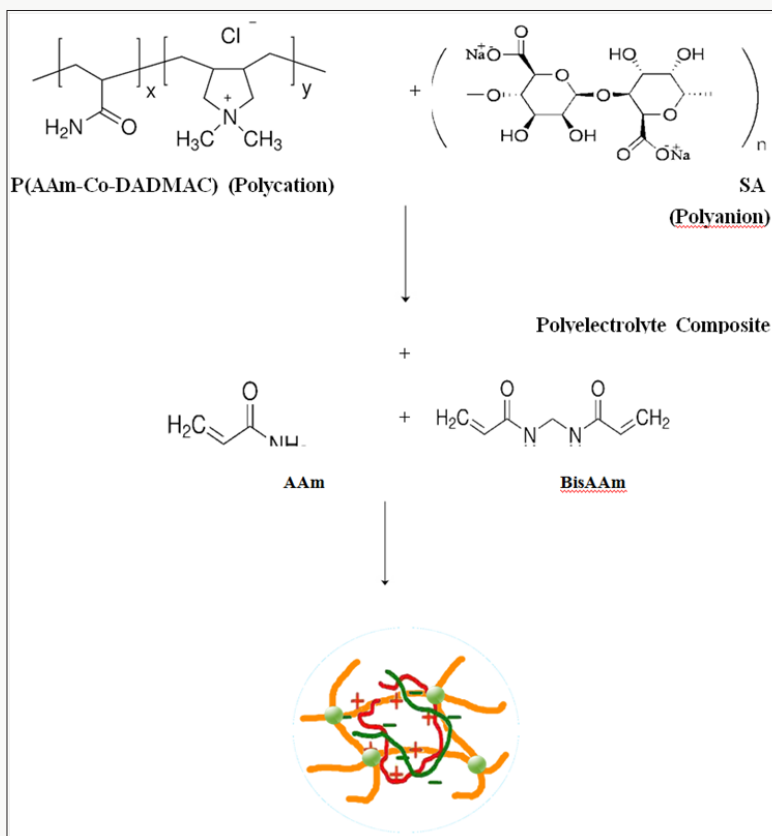
Preparation of Semi - IPN Gels (Z15-Z1)

The semi-IPNs (Z1-Z15) which loaded with Gabapentin were prepared from two components. The first constituent consisted of sodium alginate with copolymer (acrylamide–co–diallyl dimethyl ammonium chloride) (AAm-Co-DADMAC) to form polyelectrolyte structure While the second component is cross linked poly acryl amide. 1g of sodium alginate was dissolved in 15 mL of distilled water at 45oC with stirring then 0.2g of Gabapentin,1 mL of copoly (AAm-Co-DADMAC) solution in 10 ml of distilled water were added with stirring until the solution becomes homogenous then2 g of acryl Amide and (0.2 g) of bisacrylamide as cross linker in (5 ml) distilled water were added with stirring and finally 1% sodium per sulphate (10% w/v in distilled water) was added as initiator for polymerization reaction and mixed followed by addition 50μl from N,N,N,N-tetra methyl ethylene diamine as accelerator to the decomposition of initiator with stirring for ten minutes to complete the polymerization reaction. The resulting gel is cut into pieces close to the weight and washed with water once and then left to dry at 30 °C and kept in incubator at 20 oC till used. Table 1 shows the quantities that used in the preparation semi-IPN composite hydrogels Z1 to Z15, Scheme 1 shows the chemicals equations for polymerization reactions and Figure 1 showed the photograph of Z1, (Scheme 1).

Table 1: The composition used in the preparation of semi-IPNs Z1-Z15.

Sample	P(AAm – co – DADMAC)	Sodium alginate	Drug	AAm g	Bis AAm g	Ratio Copolymer and SA: AAm
		g	g			
Z1	1	1	0.2	2	0.2	1:01
Z2	1	2	0.2	3	0.3	1:01
Z3	1	3	0.2	4	0.4	1:01
Z4	2	1	0.2	3	0.3	1:01
Z5	3	1	0.2	4	0.4	1:01
Z6	1	1	0.4	2	0.2	1:01
Z7	1	2	0.4	3	0.3	1:01
Z8	1	3	0.4	4	0.4	1:01

Z9	2	1	0.4	3	0.3	1:01
Z10	3	1	0.4	4	0.4	1:01
Z11	1	1	0.6	2	0.2	1:01
Z12	1	2	0.6	3	0.3	1:01
Z13	1	3	0.6	4	0.4	1:01
Z14	2	1	0.6	3	0.3	1:01
Z15	3	1	0.6	4	0.4	1:01

Scheme1: the polymerization reactions for preparation of semi-IPNs;──poly acrylamide network , ──Sodium alginate, ──copoly (AAm-Co-DADMAC),●crosslinking poin.

Figure 1: photograph of Z1.

Preparation of The Simulated Stomach Fluid And The Simulated Intestinal Fluid

The simulated stomach fluid (SGF) and the simulated intestinal fluid were prepared according to the US Encyclopaedia of Drugs [19].

Determination of Standard Calibration Curves For Capapentin

The λ max was determined for Gabapentin which showed absorption at (202 nm) in distilled water and (201 nm), (204 nm) in SGF and SIF respectively Then, the standard calibration curves of the drug were determined.

Results and Discussion

The swelling ratio of the prepared semi-IPN hydrogels was measured as a function of time in distilled water, SFG and SIF at 37°C. The polymer compositions were weighed with a weight of 0.5 g, during certain periods of time, the samples were removed from the solution and placed on the filter paper to remove the solution from the surface (Interfacial solutions) and weighed to calculating the swelling ratio. The swelling ratio was calculated within 24 hours based on the following equation [20]:

$$\%Q = \frac{Ws}{Wd} \times 100$$

Whereas; Q = swelling ratio, Wd, = dry weight of hydrogels and Ws, = the weight of the swollen hydrogels.

The results in Figures 2- 4 indicate that the polymer compositions reach to the swelling equilibrium after 6 hours however the experiment continued for 24 hours. Semi-IPN Z1-

Z15 was loaded with Gabapentin. Copolymers were selected and sodium and acryl amide were selected. Acryl amides are formed by bonding, linear copolymers and sodium alginate. There is a simple ionic interference between the linear copolymer as a weak poly action with sodium nitrite as a strong poly anion to form the polycarbonate structure, which interferes with the formation of the second linear component of the quasi-retina structures prepared.
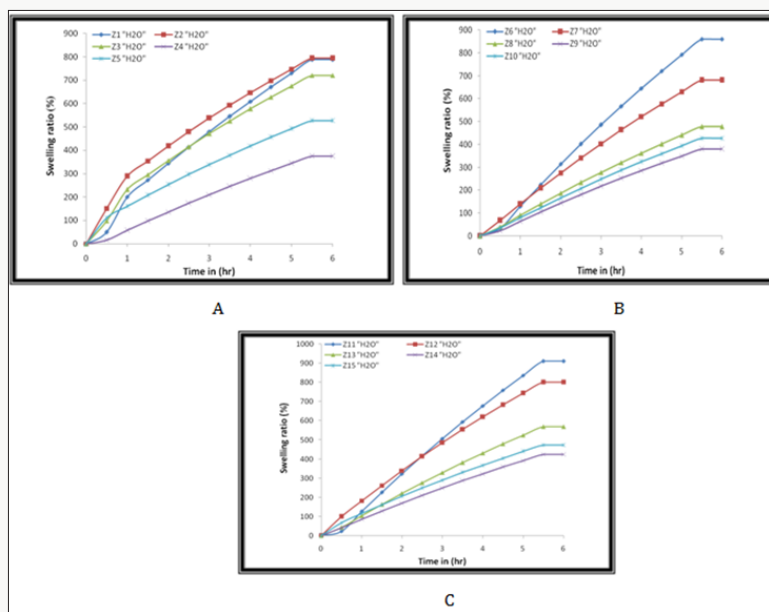

Figure 2: The swelling ratio of Semi-IPN in distilled water; A) Z1-Z5, B) Z6-Z10 and C) Z11-Z15.
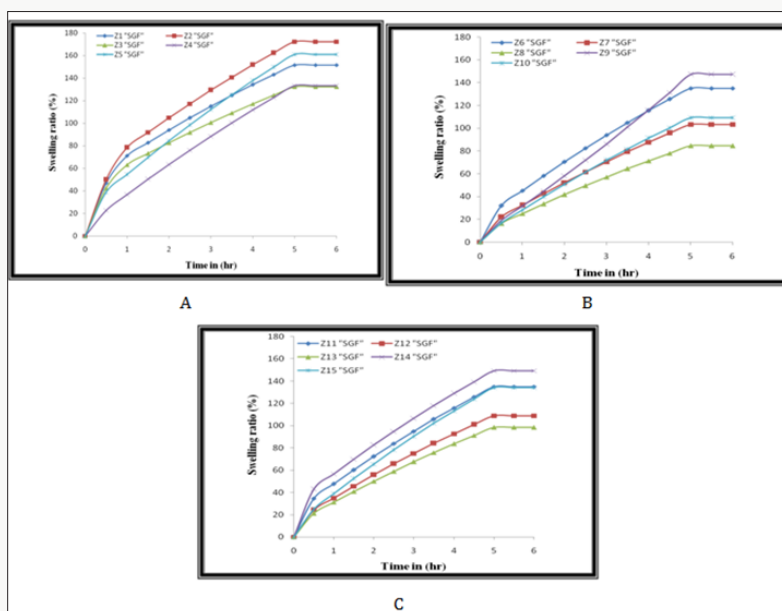

Figure 3: The swelling ratio of Semi-IPN in SGF;A) Z1-Z5 , B) Z6-Z10 and C) Z11-Z15.

(Figures 2-4) were showed high swelling ratio (SR) in both distilled water and SIF due to the presence of carboxylic group anions (- COO-) along the polymer chains of sodium alginate, leading to increased electrical repulsion between the negative

charge and then occur a high swelling process for cross linked poly acrylamide network [21-23] as well as the presence of hydrophilic groups such as (-CONH2, -N+R4) in the semi-IPNs of Z1-Z15 compositions, have an important effect on swelling behaviour

and play an important role in the rate of swelling due to increase hydrogen bonding between polymer networks and water. On the other hand, in the SGF, the semi-IPNs were showed a low swelling ratio due to the protonation of the carboxylate groups in the acid medium lead to coiling of sodium alginate chains around itself and this is enhanced by the non-expansion of the poly acrylamide network structure [21] so the resulting swelling is because of the presence of amide and ammonium groups. In general, there are a number of interactions in the acrylamide network such as ionic interference from polyelectrolyte and hydrogen bonding interference, the amide groups in the poly acrylamide network, work together to form internal hydrogen bonds. These bonds are used to form a stable shell around the ionic groups on both of the polyelectrolyte and then the acrylamide network works to pull the water (water uptake WU) from the environment [24.25]. It was found that the quaternary ammonium groups of copolymers and carboxyl groups in the sodium alginate enhance the change in the swelling ratio in SGF, SIF and distilled water. This can be useful for optimizing the applications of these polymers to the release of drugs or as biomaterials [26].
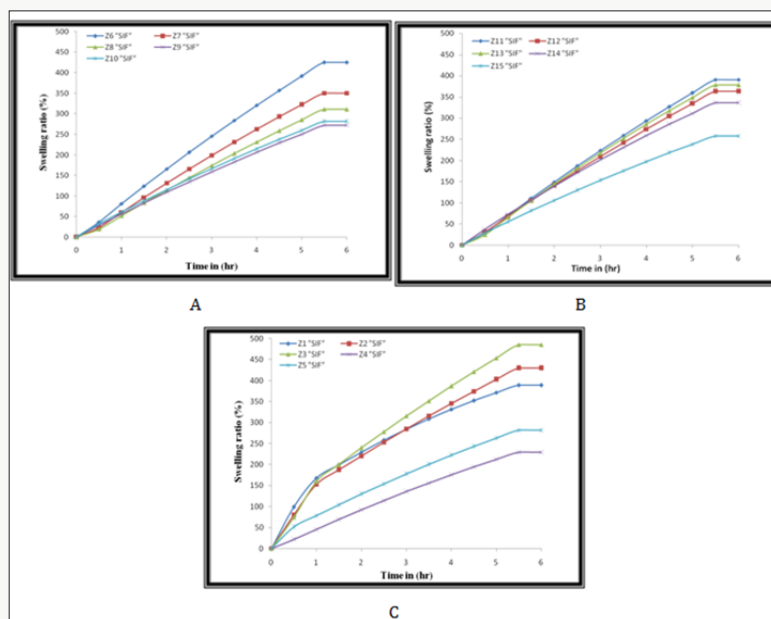

Figure 4: The swelling ratio of Semi-IPN in SGF; A) Z1-Z5, B) Z6-Z10 and C) Z11-Z15.

The external surface morphology of semi-IPNs was studied by the scanning electron microscopy. As in (Figure 5), where the images A and B represent the dry state of the Xerogel structures and swollen gel of Z7 respectively, we observe that they have a smooth compact surface as a result of the completion of the cross linking process of poly Acryl Amide while the swollen state possessed the same fine surface properties and pore sizes ranging from 169.9-45.48 micrometres.
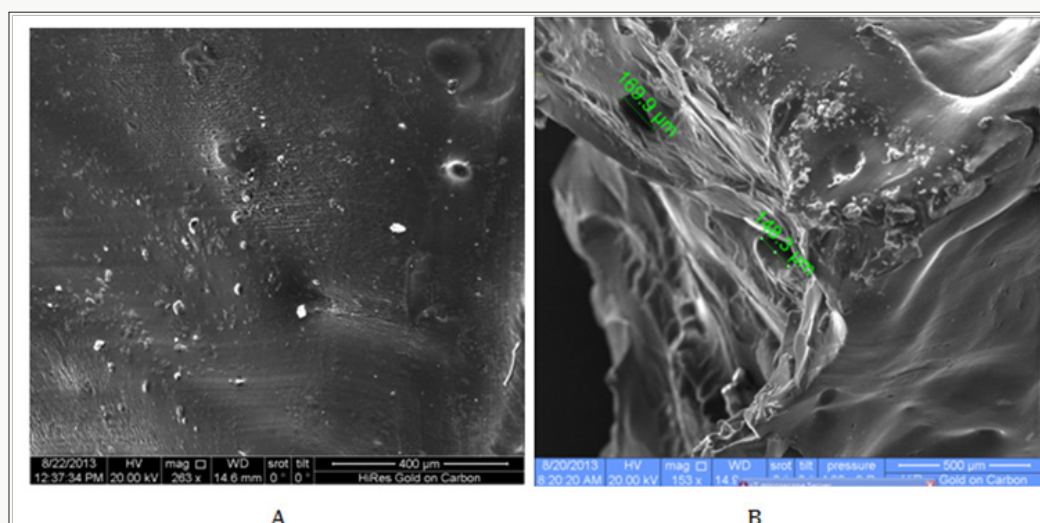

Figure 5: SEM micrograph of A) the xerogel state of Z7 B) swollen state of Z7.

The % released of Gabapentin with time was studied at (37 °C) for six hours, (Figures 6-8) shows the results of this study, the results were showed that there are no significant differences in the rate of release of the drug when immersing these hydrogels in distilled water, SGF and SIF. On the other hand, the prepared semi-IPNs were loaded with different amounts of Gabapentin (0.2, 0.4 and 0.6 g) and it was found that there is no significant effect of the change in the amount of drug loaded in the prepared hydrogels due to large pore size of the swollen hydrogel leading to the formation of channels within the polymer structures allowing the drug to pass through it to the medium. For this reason, the release of the drug depends on the mechanism of swelling followed by diffusion which is commonly used in gels polymers. This explanation is confirmed by the relatively rapid release of the drug.
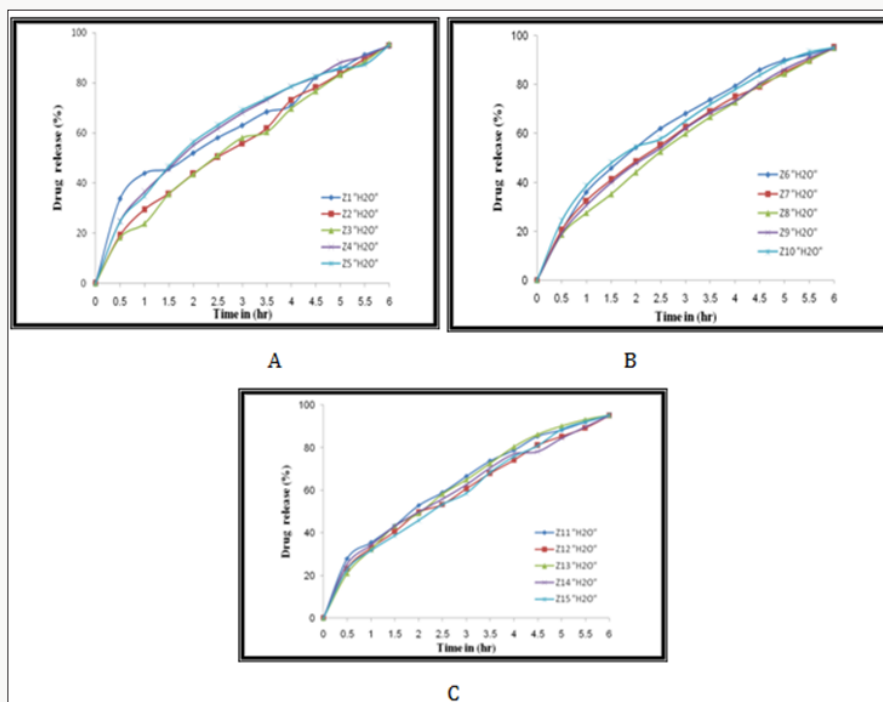

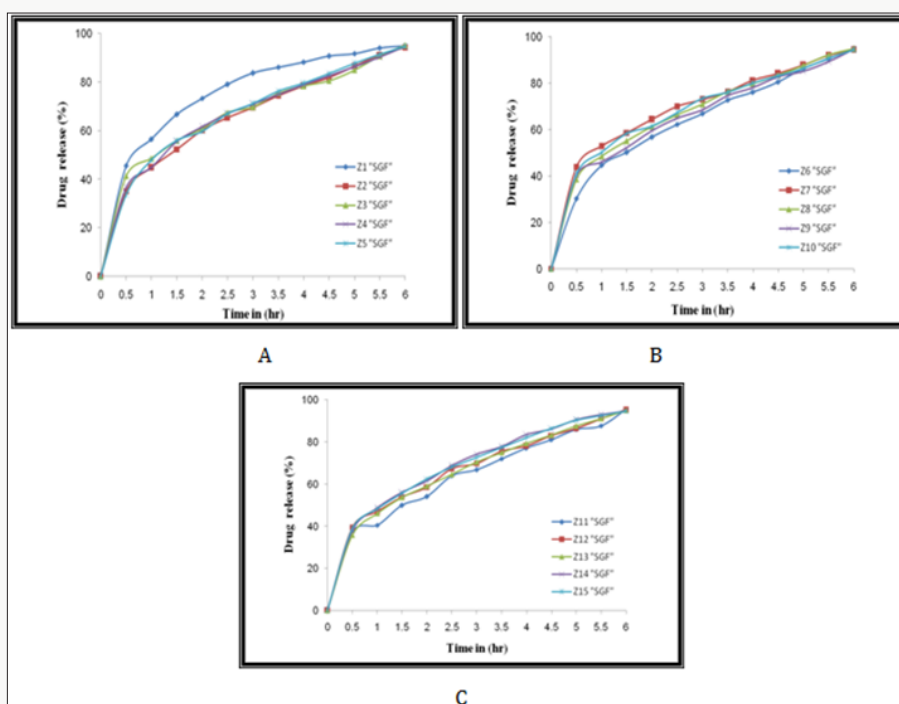**Figure 6:** The %Release of Gabapentin from: A) Z1-Z5, B) Z6-Z10 and C) Z11-Z15,in distilled water.

Figure 7: The %Release of Gabapentin from: A) Z1-Z5, B) Z6-Z10 and C) Z11-Z15, in SGF.
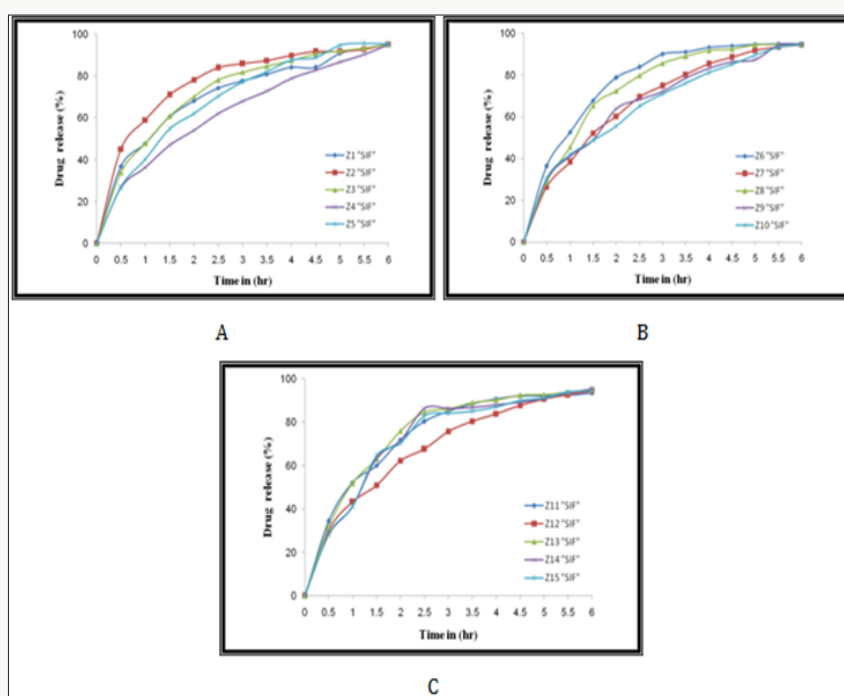
Figure 8: The %Release of Gabapentin from: A) Z1-Z5, B) Z6-Z10 and C) Z11-Z15, in SGF.

The Higuchi release equation, which is one of the simplest mathematical equations, was used to determine the ratio of the absolute amount of the drug as a function of time based on the practical results obtained from the study of the release of the Gabapentin from all of the prepared hydrogel semi-IPN in distilled water, SGF and SIF and the Higuchi constant was determined according to the following equation [27]:

$$Q_{(t)} = K_H t_{1/2}$$

Whereas:

$Q_{(t)}$: the cumulative percentage of the drug released at time t.

k_H: Higuchi dissolution constant. and

t: Time in hours.

(Figure 9) illustrates the results of the application of the Higuchi equation for the semi-IPNs Z1-Z5. (Table 2) shows the Kinetic parameters of the release curve showing best fit with higher correlation with the Higuchi's equation for Z15-Z1 in distilled water, SGF and SIF.

Figure 8: The %Release of Gabapentin from: A) Z1-Z5, B) Z6-Z10 and C) Z11-Z15, in SGF.

Table 2: Kinetic parameters of the release curve showing best fit with higher correlation with the Higuchi's equation for Z15-Z1 in distilled water, SGF and SIF.
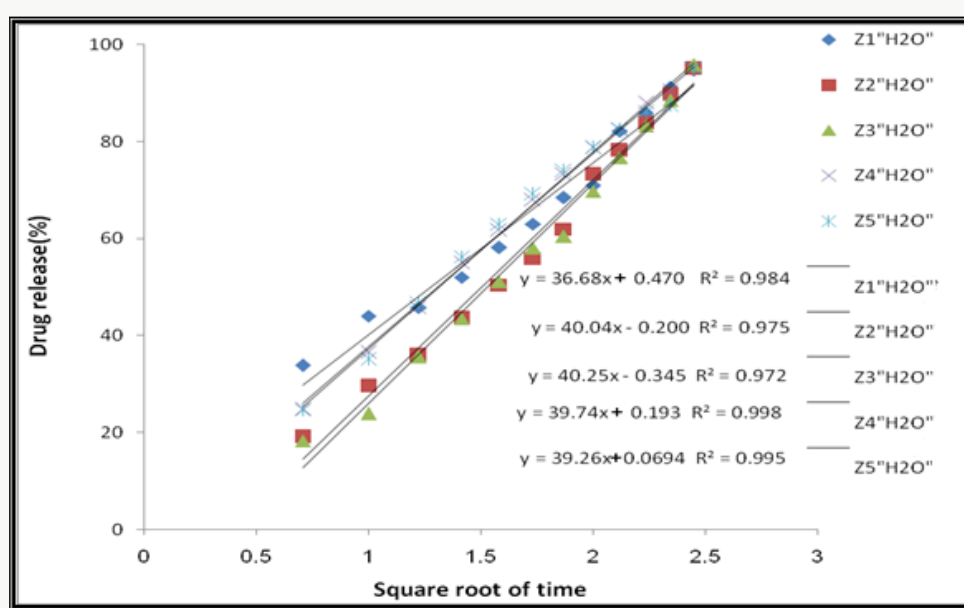
Sample	(H$_2$O)		(SIF)		(SGF)	
	R^2	R^2	KH	R^2	KH	R^2
Z1	36.68	0.984	36.04	0.929	37.27	0.968
Z2	40.04	0.975	36.66	0.991	35.66	0.896
Z3	40.25	0.972	34.97	0.973	38.80	0.959
Z4	39.74	0.998	36.27	0.986	39.20	0.998
Z5	39.26	0.995	36.92	0.988	41.39	0.986
Z6	40.28	0.994	37.16	0.995	38.99	0.915
Z7	40.02	0.992	34.86	0.962	40.87	0.988
Z8	40.81	0.980	34.86	0.962	40.52	0.939
Z9	40.62	0.988	35.54	0.982	39.33	0.989
Z10	39.93	0.996	35.22	0.927	39.21	0.997
Z11	40.01	0.995	36.44	0.989	36.61	0.938
Z12	39.44	0.991	36.04	0.983	39.53	0.989
Z13	40.30	0.989	36.85	0.991	39.24	0.926
Z14	38.93	0.995	37.28	0.985	40.21	0.923
Z15	40.64	0.982	37.00	0.984	39.92	0.936

Conclusion

The interaction between electrolytic polymers did not form a gel due to the unequal charge density, ionic strength and molecular weight of the electrolyte polymers which used in the preparation. The quaternary ammonium groups of copolymers and carboxylic groups in sodium alginate were found to enhance the change in the swelling ratio in distilled water, SGF and SIF. The SEM micrograph for swollen models showed the presence of large pores that increased the speed of release of the drug to environment.

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