1. Introduction

The hydrogels since their discovery by Wichterle and Lim in 1960 [1] have been of great interest to biomedical scientists, especially for their unique property of exhibiting an intermediate behavior between solid and liquid materials [2] . They are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids and retaining large amount of fluids in the swollen state [2] . Hydrogels can be classified as neutral or ionic, based on the nature of side groups [3] and prepared either by chemical crosslinking (crosslinking of polymers, copolymerization/crosslinking reactions, crosslinking by high energy radiation and crosslinking using enzymes [4,5]) or by physical crosslinking (crosslinking by ionic interactions[4], crosslinking by crystallization[6], crosslinking by hydrogen bonds[7] and by protein interaction[4]). For most medical application , the novel engineering of hydrogels for drug delivery require dividing them to biodegradable hydrogels which are favoured over non-degradable hydrogels since they degrade in clinically relevant time scale [8], smart hydrogel or stimuli-sensitive hydrogel that respond to environmental changes, such as temperature, pH, light, and specific molecules such as glucose [9] and finally biomimetic hydrogels which are relatively inert polymer chains can be tailored with the selected biological moieties to yield bioactive hydrogels [10].

Interpenetrating polymer networks (IPNs) are unique class of polymer alloys consisting of two (or more) cross-linked polymers with no covalent bonds or grafts between them. These mixtures of cross-linked polymers are held together by permanent molecular entanglement [11] .

Chitosan polymer is a cationic polysaccharide comprising copolymers series of glucosamine and N-acetylglucosamine. It was produced by alkaline N-deacetylation of chitin . Being natural biodegradable and biocompatible , chitosan has been used in the formulation of drug delivery to control the release system [12]. Also, researchers reported that chitosan polymer has some of pharmacological activities such as: anticoagulant [13] and antimicrobial activity [14].

It is well known that chitosan-based gels included four classes. The first is hydrogen bond complexes or covalently crosslinked chitosan hydrogels which can be divided into three types: chitosan cross-linked with itself [15] , hybrid polymer networks (the cross-linking reaction occurs between a structural unit of a chitosan chain and a structural unit of a polymeric chain of another type) and semi- or full- IPN [16] . The second class is coordination complexes or ionically crosslinked chitosan hydrogels in which the entities reacting with chitosan are negatively charged components (ions or molecules), forming a network through ionic bridges between polymeric chains [17] .the other two classes are grafted chitosan hydrogels and polyelectrolyte complexes [18].

2. Materials And Methods

Chitosan (medium molecular weight), Sigma chemical co. (Aldrich), USA. Polyvinylpyrrolidone (M.W. 40000, powder), Fluka analytical, USA. Polyvinylpyrrolidone (M.W. 160000, solution), Fluka analytical, USA. Polyvinylalcohol (M.W.89000-98000), Sigma chemical co. (Aldrich), USA. Glutaraldehyde (50% solution in water), Merck – Schuchardt, Germany. All other reagents were of analytical grade.

2.1 Preparation of hydrogel

Synthesis of hydrogels

Chitosan solution (2%, w/v) was prepared by dissolving chitosan in 0.1M acetic acid. Glutaraldehyde solution (0.4% v/v) was used in the synthesis of hydrogels by crosslinking of chitosan with dialdehyde using solvent casting method [19].

In the preparation of formulas 1, 2, 3, 4, 5, 6, 7 and 8 (table 1), polyvinylpyrrolidone (PVP) solution (M.W. 40000, 4%, w/v) was prepared in

deionized distilled water and blended with chitosan solution in different proportions. Gluteraldehyde solution was added to chitosan – PVP blend to form semi-IPN with different crosslinking degree. The formed hydrogels were casted in several size petri dish and dried by allowing the solvent to evaporate in an incubator at 37ºC for 72 h. After drying they were soaked in 0.1N NaOH solution for 5 min, washed with absolute ethanol washing two to three times and dried at 45 ºC for 24 h [19].

Calculation of crosslinking degree

The degree of crosslinking was used to determine one of the most important factors affecting drug release .
The amount of chitosan amine groups (NH_2) can be determined using the following expression [21]:

$$n_{(GluN)} = \frac{m_{(CTS)}}{\left[M_g + \frac{1-DD}{DD} M_a\right]} \quad \text{..... (2-1)}$$

Table 1 : Different Formulas of IPN Using Different PVP Grades

No.	Proportion of chitosan (2%w/v) (ml)	Proportion of PVP 40KD (4%w/v) (ml)	Proportion of PVP 160KD (4%w/v) (ml)	Proportion of PVA (4% w/v) (ml)	GA (0.4%v/v) (µl)	Crosslinking degree
Air dried formulas						
F1	10	0			71	0.63%
F2	5	5			35	0.63%
F3	3	7			21	0.63%
F4	7	1.5			50	0.63%
F5	7	1.5			150	1.9%
F6	7	1.5			300	3.8%
F7	7	3			50	0.63%
F8	7	4.5			50	0.63%
F9	7		1.5		50	0.63%
F10	7			3	50	
Freeze dried formula						
F11	7	4.5			50	0.63%

Formula 11 was prepared as mentioned above except that the resulted hydrogels were rapidly frozen at -55ºC and then dried in the freeze-dryer for at least 15-20h.

PVP solution (M.W. 160000, 4%w/v) was used instead of PVP solution (M.W. 40000, 4%w/v) for synthesis of hydrogel formula 9.

Finally, the full-IPN was produced from crosslinking of chitosan-PVA blend by glutaraldehyde [20] as in formula 10 .

Where *Ma* = 203 g/mol and *Mg* = 161 g/mol are the molecular weights of the N-acetylglucosamine (GluNAc) and GluN units within the copolymer respectively, $m_{(CTS)}$ is dry weight of chitosan in grams, $n_{(GluN)}$ is the molar amount of amine groups in that weight of chitosan and *DD* is the degree of deacetylation.

Then, the following equation can be used to define the crosslinking degree (***x***) as the percentage of aldehyde (CHO) groups with respect to the initial free NH_2 groups (CHO/NH_2 ratio) :

$$x(\%) = \frac{n_{(CHO)}}{n_{NH_2}} \times 100 = \frac{2n_{(GA)}}{n_{(GluN)}} \times 100 \quad \text{.....(2-2)}$$

By replacement of equation (2-2) with equation (2-1), the final expression will be:

$$x(\%) = \frac{2V_{(GA)}C_{(GA)} \times \left(M_g + \frac{1-DD}{DD} M_a \right)}{m_{(CTS)}} \times 100$$

..... (2-3)

Where $V_{(GA)}$ and $C_{(GA)}$ are respectively the volume and concentration of the glutaraldehyde solutions. Actually, the crosslinking degree defined by equations 2-2 and 2-3 is the reagents feed ratio, since the real crosslinking efficiency depends upon the chemical conversion and on the occurrence of other parallel reactions, which can form either any or longer crosslinks.

The glutaraldehyde solution concentration added to chitosan solution was kept constant. The several crosslinking degrees (0.63%, 1.9% and 3.8%) were obtained by only changing the volume of glutaraldehyde solution.

2.2 *Characterization of the prepared hydrogels*

Morphological study

Photographic pictures shot by an ordinary camera of 5 megapixel-lenses were used to describe the morphological features of air- and freeze dried pieces.

FT-IR study

Spectroscopic structural elucidation of semi-IPN membranes was done by FTIR . Samples of the prepared hydrogels were grinded, mixed with potassium bromide and pressed in the form of disc (13mm in diameter). The disc was analyzed by shimatzu FTIR 8000 spectroscopy from 4000-400 cm^{-1} [22].

Swelling study

In order to study the swelling behaviour , the preweighted dry sample was immersed in swelling solution with pH value of 1.2, 2 and 3. Empty dry baskets were weighted. The basket's rotation speed was set at 100 rpm. At 15 min. time intervals, the samples were removed from the swelling medium and blotted on piece of filter paper prior to weighing to remove excess surface moisture. The swelling percent (S%) was determined according to the following expression [23, 24]:

$$S\% = \frac{W_t - W_d}{W_d} \times 100 \quad \text{.....(2-4)}$$

Where W_d is the initial dry weight (g) of the sample and W_t is the weight (g) of the swelled sample at specific time (t). The term swelling fold (SF) where utilized instead of S% by dividing by 100 to illustrate and discus the results.

Statistical analysis

The results of the experiments were given as a mean of triplicate samples ± standard deviation and were analyzed according to the analysis of variance (ANOVA) test at level of (P<0.05) and (P<0.01).

3. *Results and discussion*

3.1 *Preparation of polymer network*

The network engineering relies on the generating of association among the polymer chain to establish three dimensional matrix which could be physical or chemicals and could be among the chain of the same or different polymers [25].

In the case of chitosan / PVP semi-IPN, only chitosan crosslinked with glutaraldehyde to form a network as PVP was not involved in the chemical reaction providing physical entanglement of the free polymer with the network. While in the case of chitosan / PVA IPN, the two polymers were involved in crosslinking by glutaraldehyde providing entanglement of the two networks .During the reaction of chitosan with glutaraldehyde, the amino group of

N-acetylglucosamine moiety of chitosan form imine bond (C=N) with aldehyde group. Whereas in the reaction of PVA with glutaraldehyde, the free alcoholic hydroxyl react with aldehyde group [20] .

3.2 *The morphological characteristic of the hydrogel*

The photographic pictures of freeze- and air-dried hydrogels are illustrated in Figures 1A and 1B respectively .

The resulted freeze-dried formula acquire the shape of the container that prepared in it , so it can be divided into many three-dimensional pieces. As observed in the figure 1A , the prepared hydrogel has off-white colour with rough and wrinkle surfaces. This is due to the presence of pores that become connected to each other toward the core of the matrix forming large , open and interrelated channel-like scaffold which generates separated layers of network resulting in preparation of formula with sponge architecture [23] .

The air-dried formula was appeared as a single and thin membrane with a thickness of 0.1-0.5mm depending on the size of the blend and petri dish used . Unlike the freeze-dried formulas , it has yellow transparent colour and smooth out surfaces with no pores and hence interconnected channels [23].

It was observed in figure 1B that the prepared membrane was compact (without separated layers within its architecture) and also brittle that could be broken easily to several small pieces for handling .

A

B

Figure 1: Photographic pictures illustrating the external morphological characteristic of the **(A)** freeze-dried formulas (**F11**) and **(B)** air-dried formulas (**F8**)

3.3 FT-IR characteristic

The structural characterization of the crosslinked polymers and blends was performed by recording FT-IR spectra of the samples. The comparison between the spectrum of pure chitosan powder with glutaraldehyde-crosslinked chitosan shows the appearance of distinctive peak at 1651.21 cm^{-1} (figures 2A and 2B) which is attributed to the formation of imine linkage between aldehyde group and amino group of chitosan [19 , 26].

The increased intensity of the band at 1763 cm^{-1} is due to additive number of carbonyl groups of aldehyde (figure 2B).

FTIR spectrum of pure PVA sample is shown in figure 3A. It clearly reveals the major peaks associated with poly(vinyl alcohol). For instance, typical strong hydroxyl bands for free alcohol (non-bonded –OH stretching band at 3600-3650 cm^{-1}). Also, absorption bands at 3200-3570 cm^{-1} are expected to occure due to intramolecular and intermolecular hydrogen bonds among PVA chains [27- 29] .

By crosslinking PVA with GA (figure 3B), the O-H stretching vibration peak (3330-3350 cm^{-1}) was decreased when compared to pure PVA. This result suggests that the hydrogen bonding becomes lesser in crosslinked PVA because of the diminution in the number of free OH groups . In addition, the C-O stretching at approximately 1217.12-1100 cm^{-1} in pure PVA is replaced by a broader absorption band (1000 - 1140 cm^{-1}), which can be attributed to the ether linkage of the acetal ring (C-O-C) formed by the crosslinking reaction of PVA with GA [28-30] .

Therefore, it can be assumed that GA is acted as a chemical crosslinker among PVA polymer chains [31].

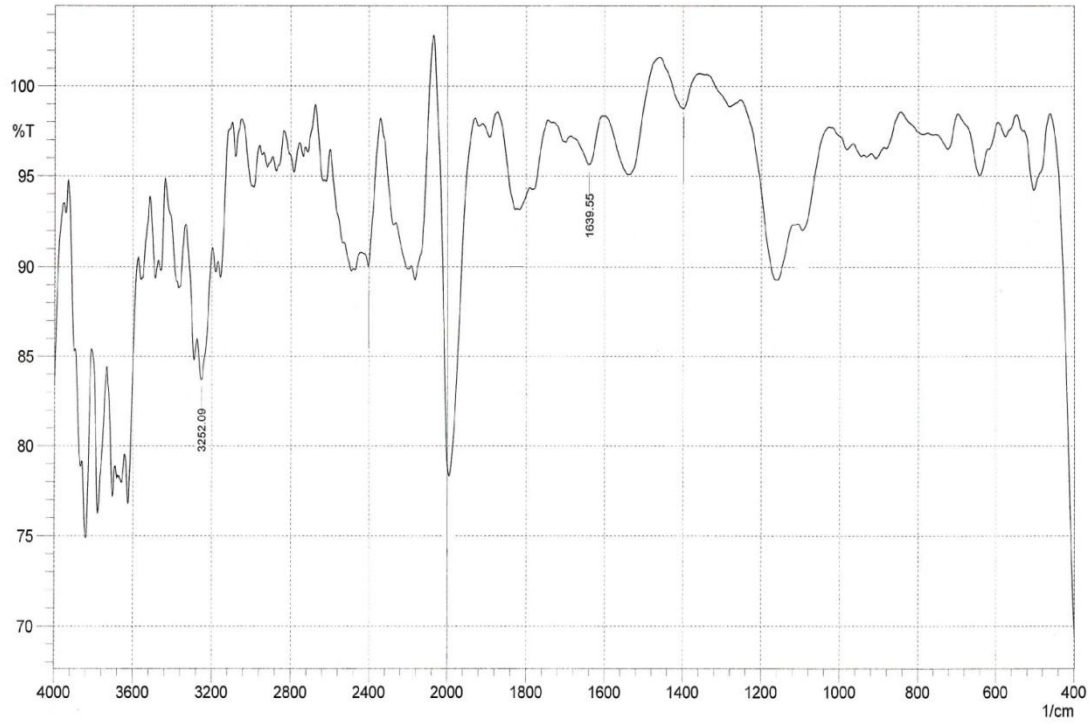
3.4 *Hydrogel swelling characteristics*

The produced hydrogels that were prepared from chitosan exhibited pH-sensitivity for swelling profile. Where chitosan polymer has a primary amino group in its N-deacetylated glucosamine units with pKa of 6.5. So protonation of $–NH_2$ will be in pH below the pKa imparting the polymer chain a positive charge along its back bone. The acquired positive charge contribute to chain repulsion, relaxation and swelling of the matrix [32,33]

The extent of network expansion is directly related to chitosan amino group protonation and hence to the availability of hydronium ion (H^+) in the dissolution media. So the decrease in the swelling ratio with increasing pH value was observed. Figure 4 illustrate that there is a significant decrease *($p < 0.05$)* in the maximum fold of swelling (MFS) from 4.75 to 2.00 folds and from 10.90 to 3.96 folds as pH increases from 1.2 to 3 for formulas F1and F4 respectively .

The preparation of formula F11 by freeze drying includes the sublimation of the freezed solvents (usually water) at -55ºC. This process produces pores and crack-like channels within the matrix, that support the diffusion of dissolution media within the hydrogel leading to rapid swelling to a very high extent (over 50.00 fold) [34]. Accordingly, as shown in figure 5, there is a significant differences ($p < 0.01$) between the freeze dried formula (F11) in different pH with corresponding air dried one (F8) in regard to swelling fold. The MFS for formulas F11 and F8 in pH 1.2 is 57.81 and 13.15 folds , in pH 2 is 53.98 and 10.25 folds and in pH 3 is 42.97 and 6.74 folds respectively.

A



B

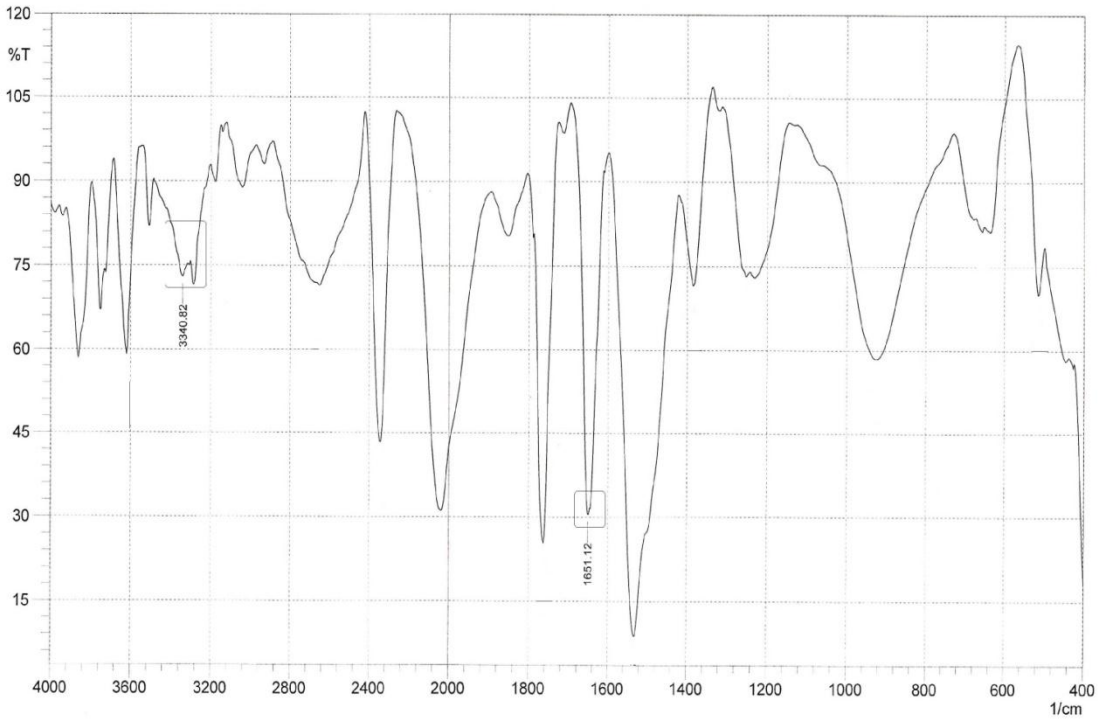
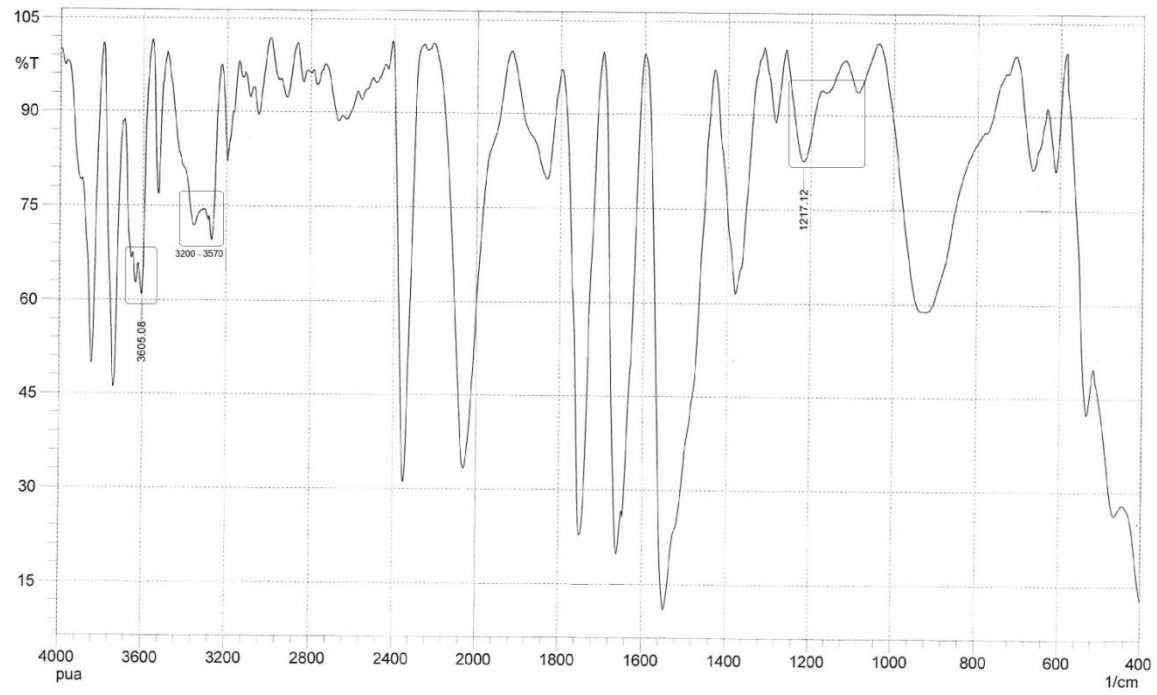


Figure 2: FT-IR spectrum of (A) non- crosslinked chitosan polymer (B) crosslinked chitosan polymer with GA

A



B

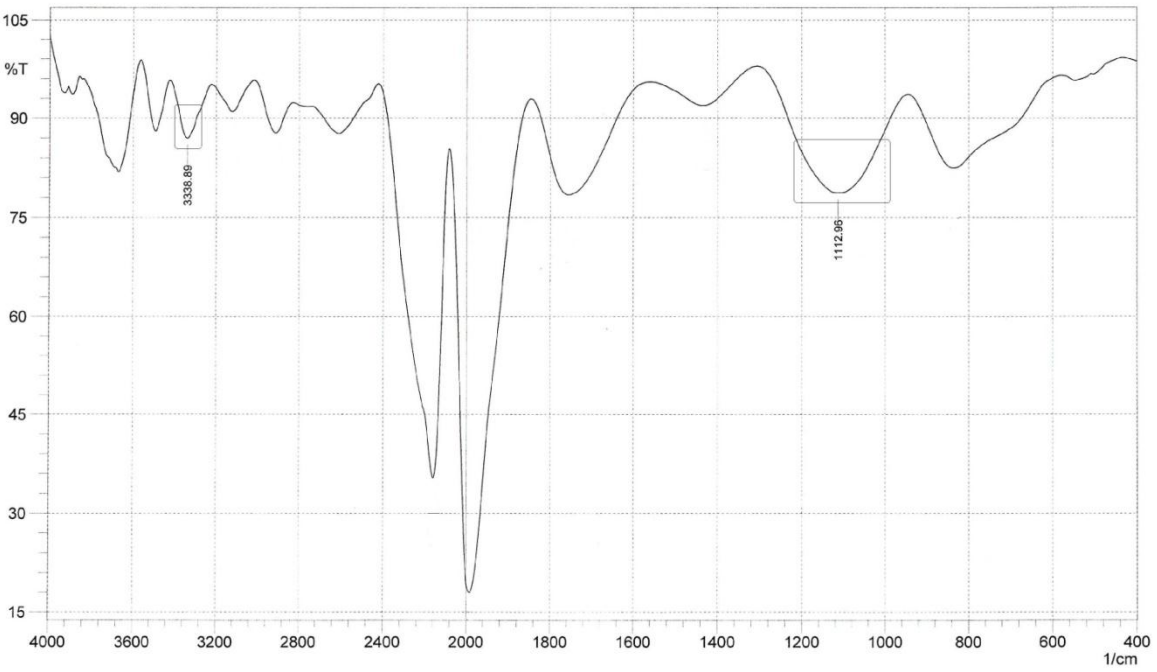
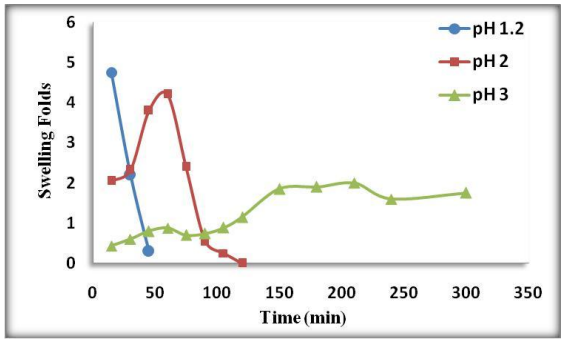


Figure 3: FT-IR spectrum of (A) non-crosslinked PVA (B) crosslinked PVA with GA

The presence of the hydrophilic PVP is responsible for the significant increase *(p < 0.05)* in the swelling fold over the pH range of the study (4.75 and 10.90 folds in pH 1.2 , 4.20 and 8.86 folds in pH 2 and 2.00 and 3.96 folds in pH 3 for formulas F1 and F4 respectively) as shown in figure 6. In the comparison of formulas F1with F9, also significant increase *(p < 0.05)* in the fold of maximum swelling but to a lesser extent which is equal to 8.84 , 6.35 and 6.71 folds in pH 1.2 , pH 2 and pH 3 respectively (figure 7). The delayed onset of swelling was also observed in pH 2 and 3. This is due to the increased length of polymer chain around the polymer-forming network preventing it from relaxation to its maximum capacity as a result of increased entanglement [35] .

A)



B)

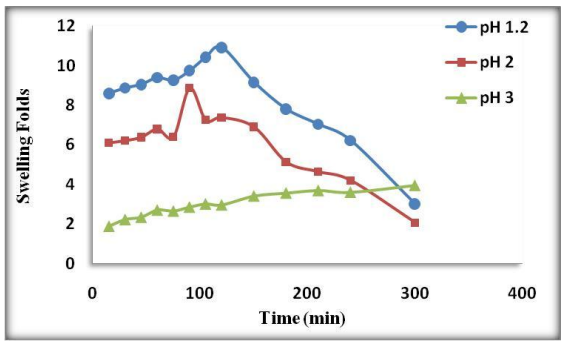


Figure 4: Effect of media pH on swelling capacity of **A)** formula **F1** and **B)** formula **F4** at 37ºC

Five different polymer ratios of chitosan:PVP [7:1.5 (formula F4), 7:3 (formula F7), 7:4.5 (formula F8), 3:7 (formula F3) and 5:5 (formula F2)] were included to investigate the effect of changing PVP content in the network. Figure 8 illustrates that increasing the amount of PVP from 1.5 to 4.5 will cause a significant increase ($p < 0.05$) in swelling fold of the prepared hydrogels where in pH 1.2 the MFS was 10.90, 11.10 and 13.15 folds for formulas F4, F7 and F8 respectively . This is because of increasing water holding capacity of the networks along with increasing the amount of hydrophilic component until certain limit beyond it the network will be dissolved rapidly as in formulas F2 and F3 where the MFS was 5.20 and 2.77 folds in pH 1.2 respectively [36,37] . Figure 9 illustrates the MFS in three dissolution media for these formulas and confirms the mentioned result.

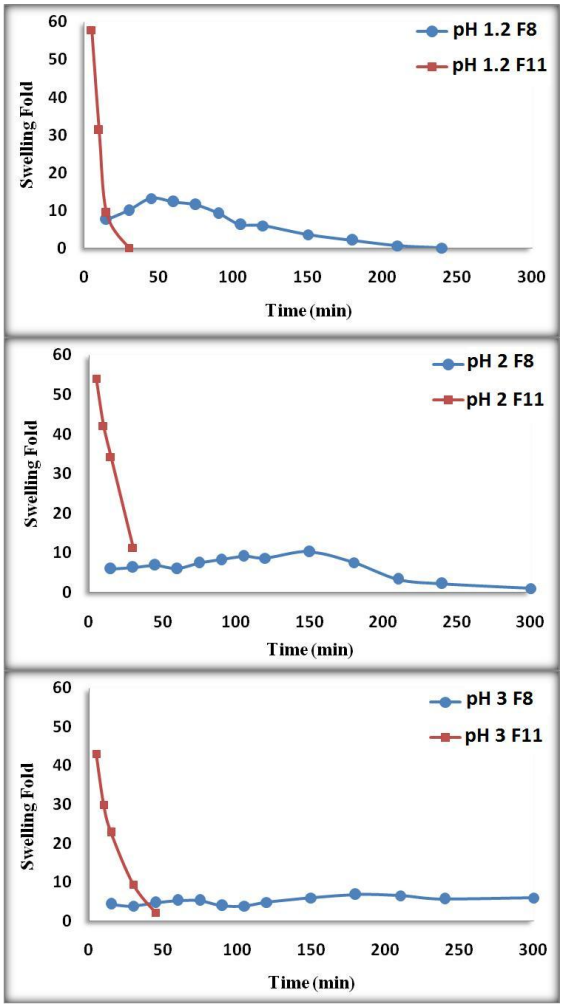


Figure 5: Effect of freeze-drying on the swelling fold of freeze-dried formula **(F11)** and air-dried formula **(F8)** at 37ºC in different pH

The crosslinking agent serves as anchoring agent that fixes or restrain the movement of the polymer network also decreases the distance between polymer chains leading to decrease the free volume available for

water solvent permeability. At the same manner, there is a significant ($P < 0.05$) decrease in the extent of network swelling from 10.90 folds to 7.61 folds in pH 1.2 and from 8.86 folds to 5.71folds in pH 2 (figure 10), unlike the increment of physical crosslinker content (PVP) which accompanied by increase in the swelling of the hydrogel. Also it is expected that gels with a greater crosslinking would swell more slowly due to the mechanical hindrance of polymer chains [38,39]. Table 2 shows the MFS with the time required to achieve it in three different pH, where in pH 1.2 it was delayed from 120min to 210min and in pH 2 from 90min to 300min. While, in regard to pH 3, it is difficult to detect a definitive MFS due to decrease in the environmental stimuli.

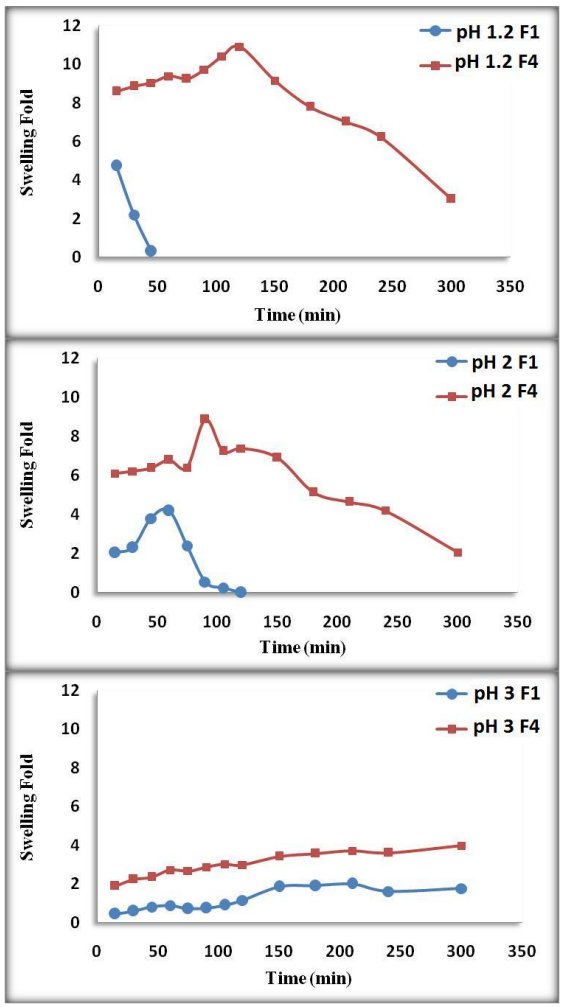


Figure 6: Effect of forming semi-IPN on the swelling fold of chitosan only formula **(F1)** and chitosan / PVP formula **(F4)** at 37ºC in different pH

The prodigious increase in the entanglement of the network by the crosslinking of both polymers with glutaraldehyde and the presence of H-bond between the free hydroxyl groups of PVA and chitosan will generate hydrogel membrane with special mechanical properties that restrict chain relaxation [40,25]. Figure 11 shows that there is a significant decrease *($P < 0.05$)* in the extent of the matrix swelling , where the semi-IPN (formula F7) swelled to 11.10 folds , 8.56 folds and 4.87 folds, while for the full-IPN (formula F10) was 2.51 folds , 2.32 folds and 1.75 folds in pH 1.2 , pH 2 and pH 3 respectively.

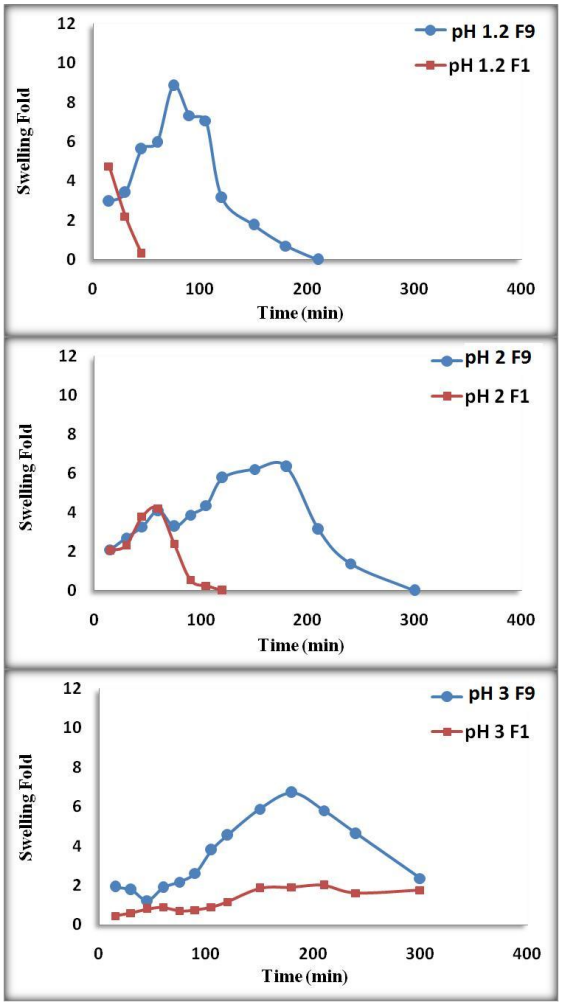


Figure 7: Effect of forming semi-IPN on the swelling fold of chitosan only formula **(F1)** and chitosan / PVP formula **(F9)** at 37ºC in different pH

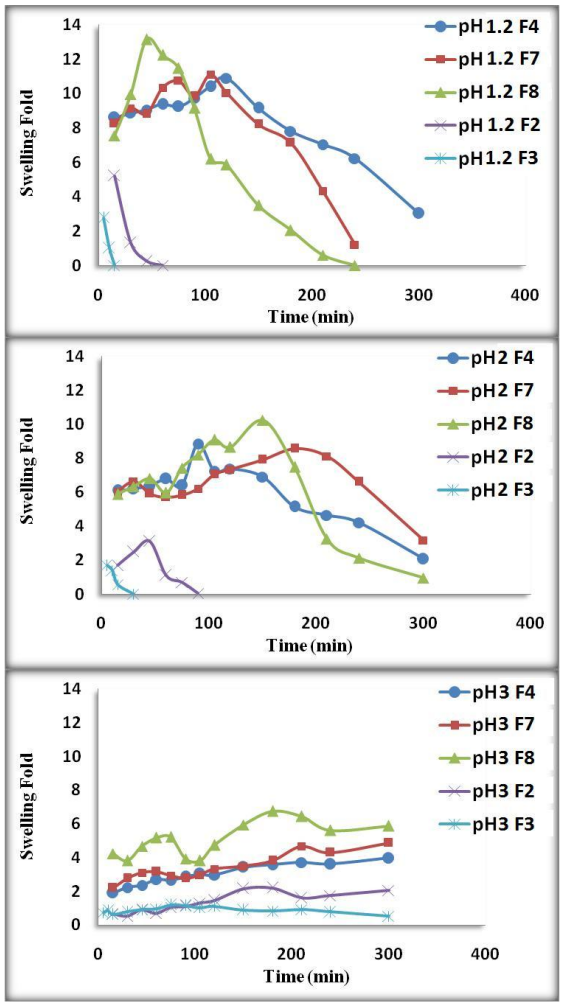


Figure 8: Effect of increasing PVP amount on the swelling fold of formulas **F4, F7, F8, F2** and **F3** at 37ºC in different pH

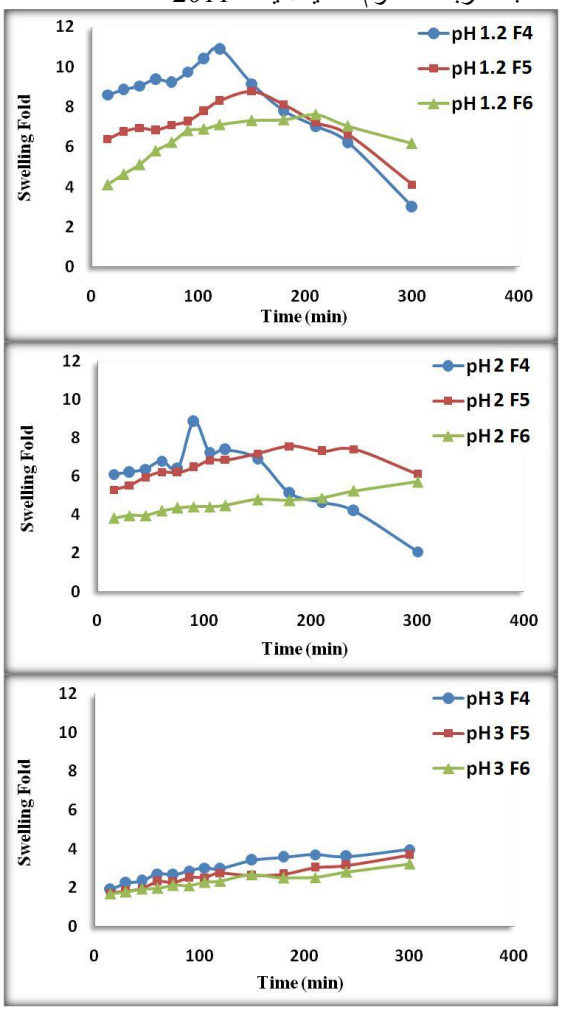


Figure 10: Effect of increasing crosslinking degree on the swelling fold of formulas **F4**, **F5** and **F6** at 37ºC in different pH

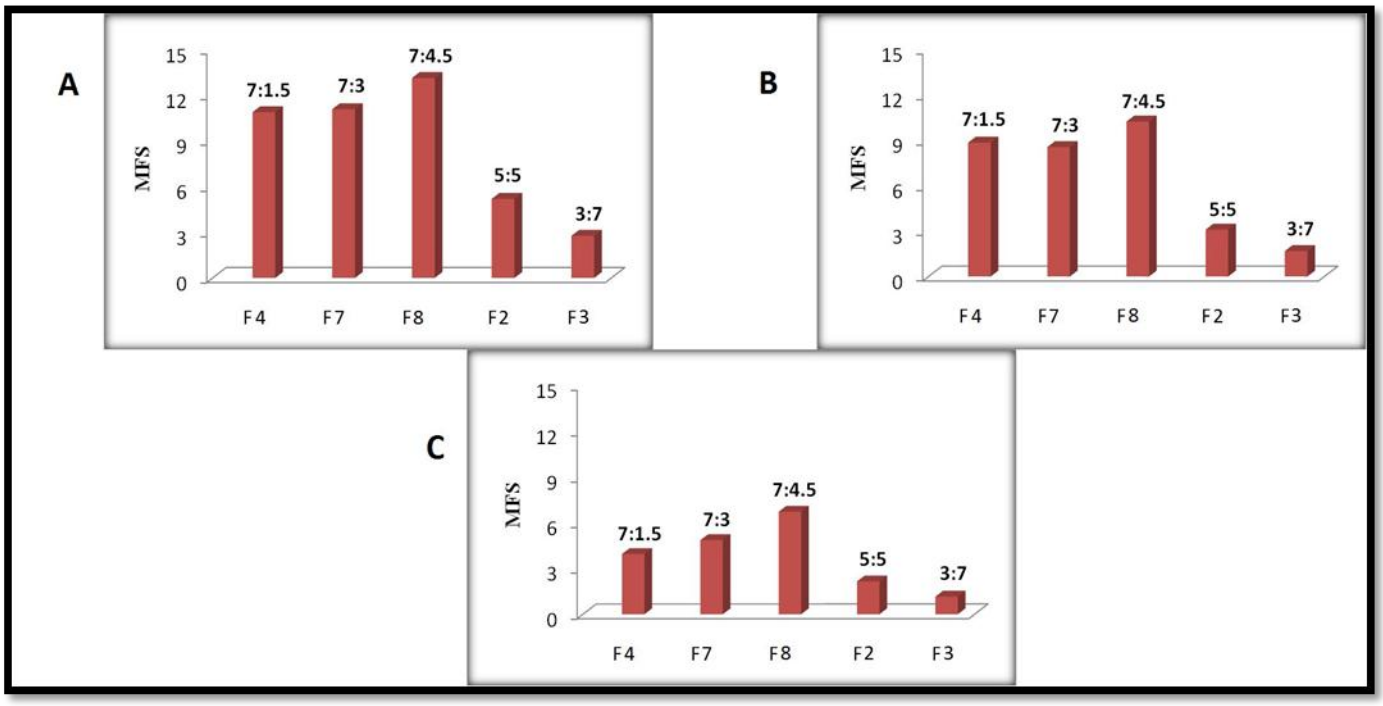


Figure 9: The maximum fold of swelling for formulas F2, F3, F4, F7 and F8 at 37ºC in **(A)** pH 1.2, **(B)** pH 2 and **(C)** pH 3

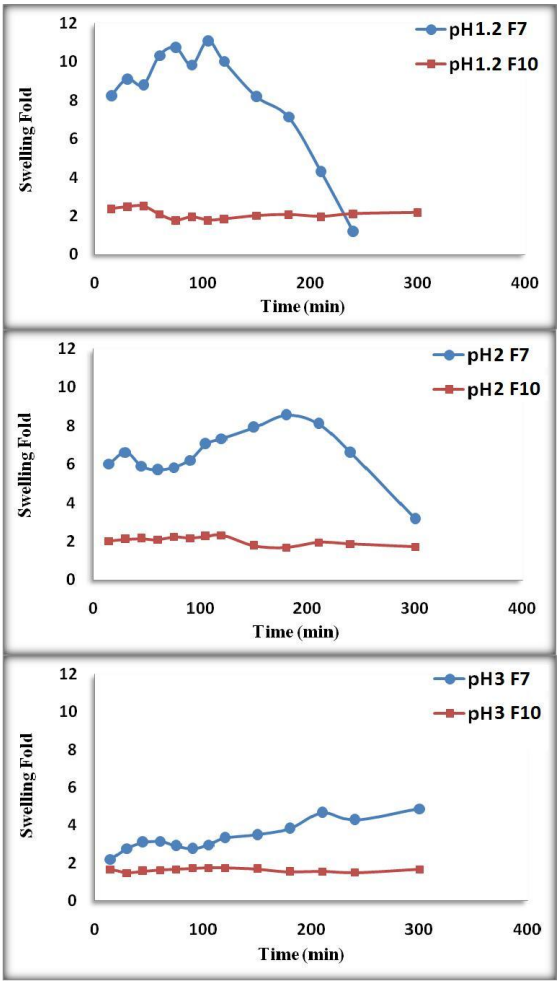


Figure 11:Effect of using PVA on the swelling fold of networks of chitosan/PVP (formula **F7**) and chitosan/PVA (formula **F10**) at 37ºC in different pH

Table 2: The Maximum Fold Of Swelling With Its Time Required To Achieve It For Increased Crosslinking Formulas **F4**, **F5** and **F6** At 37ºC In Different pH

pH value	Formula No.		
	F4	F5	F6
1.2	10.90 ± 0.21 at 120 min	8.78 ± 0.11 at 150 min	7.61 ± 0.15 at 210 min
2	8.86 ± 0.17 at 90 min	7.57 ± 0.14 at 180 min	5.71 ± 0.16 at 300 min
3	3.96 ± 0.07 at 300 min	3.68 ± 0.09 at 300 min	3.23 ± 0.04 at 300 min

4. Conclusion

Chitosan and PVP were successfully formulated as pH sensitive semi-IPN that swells at specific site (stomach) within two hours. Based on the result, all the prepared hydrogels have distinctive pH sensitivity which is due to chitosan polymer, the incorporation of PVP to form semi-IPN regulates and extend the network swelling, the increasing physical crosslinker (PVP) improve the water holding capacity and hence swelling properties while increasing the chemical crosslinker (glutaraldehyde) restrict the water holding capacity and definitely the extent of swelling. For the future, it can be designed to control the release of drugs in stomach for local or systemic indication.

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