ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

# Development of Gastroretentive Drug Delivery Systems Based on N-Isopropylacrylamide Hydrogels

**Rubab Zohra[1]* and Muhammad Aslam Malana[2]**

[1]*Professor, Department of Chemistry, Forman Christian College, Lahore, Pakistan*

[2]*Professor, Chemistry Department, Bahauddin Zakarya University, Multan, Pakistan*

***Corresponding Author:** Rubab Zohra, Professor, Department of Chemistry, Forman Christian College, Lahore, Pakistan.

**Received:** December 11, 2017; **Published:** January 24, 2018

## Abstract

It was planned to synthesize dual-responsive hydrogels from N-isopropyl acrylamide (NiPAAm), methacrylate (MA) (to attain required mechanical strength) and acrylic acid (AA), as a major hydrophilic component. Hydrogels were prepared by free radical copolymerization using ethyl alcohol as a solvent. Benzoylperoxide (BPO) was introduced as initiator and diethylene glycol dimethacrylate (DEGDMA) and ethylene glycol dimethacrylate (EGDMA) as chemical cross linking agents. Network parameters like polymer mesh size (ξ) (23.78 to 820 Å), molecular weight between the cross-links (Mc) (970-356096 $gmol^{-1}$) and crosslink density (q), (0.0928 to 0.00025) were calculated at various pH using the Flory-Rehner Theory. Hydrogels exhibited the non-Fickian diffusion mechanism. FTIR spectral analysis and (TGA/DSC) were carried out to characterize the systems and new LCST was found to be increased. The active agent loading and release attitudes of gels were investigated for Tramadol HCl. Conclusively, these systems exhibited a distinctive transition in their media sorption capacity with the surrounding pH and temperature, recommending them as strong candidates as oral drug delivery systems. The results favored the idea to apply these hydrogels to use as targeted drug delivery systems for proximal part of gastro-intestinal tract.

***Keywords:*** *Gastro Retentive; Drug Delivery; Hydrogels; N-Isopropylacrylamide; Dual- Responsive*

## Introduction

The formulation of oral drug delivery vehicles tuned to target the colon, are prone to damage by proteolytes of the stomach and absorption in upper region of small intestine. Since, such drug systems have attained enhanced significance not only for the drug release during the treatment of colonic diseases, but also for being potentially capable for protein and therapeutic peptide deliveries.

Stimuli-sensitive hydrogel approaches; ability to undergo a remarkable change in their behavior under the effect of external stimuli (e.g. temperature, electrical field, pH, chemical substances or ionic strength), have been successful in designing drug release systems [1-7]. Among all, thermo and pH-responsive hydrogels have been especially focused by the researchers. But the drug release of the designed formulations is still debatable [8-10]. Many factors like dynamic and equilibrium degree of swelling of hydrogels, relative interactions between drug and a specific polymer system, the dissolution of the drug in the release solvent and penetration of drug throughout the polymeric network, govern drug release from delivery systems.

Poly (N-isopropylacrylamide) (PNiPAAm) based hydrogels exhibit volume phase transition in aqueous medium around 32oC (lower critical solution temperature or LCST) and hence, have gained special attention of research community [11-13]. Many scientists believe that to match of the formulation with the desired critical region is obtained by the adjustments of LCST by varying ratios of hydrophilic and hydrophobic components of the polymer formulation. It was stated by Yildiz and his co-workers that the LCST shifts to lower temperatures due the hydrophobic ingredients and to the higher temperatures due to the hydrophobic components [14].

Model drug, used in our investigations, tramadol HCl is quite safe to cardiovascular or respiratory parts and is capable to deal with both *in vitro* and *in vivo* pains [15]. The formulation and the release behavior of novel drug delivery systems based on N-isopropylacrylamide (NiPAAm) were studied in detail following various experimental variations.

## Experimental Section

### Materials

Chemicals used in the present project were as follows: Acrylamide and Methacrylate (both were 99%, MERCK), Acrylic acid (99%, Fluka), Ethylene glycol dimethacrylate (100%, Fluka) and Diethylene glycol dimethylacrylate (95%, ALDRICH), Sodium acetate (99%, Kanto Chemical Co.), Benzoyl peroxide and Citric acid (100% each, MERCK), Acetic acid (100%, Riedol-Dehaen), HCl (37%, Merck).

### Preparation of Hydrogels

Chemically cross-linked co-polymers of N-isopropylacrylamide (NiPAAm), acrylic acid (AA) and methacrylate (MA) were prepared by free radical polymerization mechanism. In a typical preparation, the monomers NiPAAm, MA and AA (1g, 1.5 ml and 1.5 ml, each) were taken in a glass tube supported with a screw cap. In every sample 0.5 ml of crosslinking agent, 5 ml of solvent (ethyl alcohol) and 0.01g of initiator (benzoyl peroxide or BPO) were added to the monomeric mixture. Nitrogen gas was passed through the mixture to prevent undesirable interaction of oxygen. After that, the tubes were adjusted in a thermostat preset at 25oC. Details of heating scheme have been published [16]. The polymeric column started to build up at 70oC and incubated for 6 - 8 hrs at the same temperature to allow completion of the reaction. Column was removed from the screw capped tubes and cut into specimen disks (approximately 1 - 2 mm thick). Any unreacted materials were removed by washing the disks with deionized water. Before preserving for further study, the disks were slow dried under room conditions.

### Characterization

The synthesized NiPAAm based hydrogels were characterized by FTIR (Fourier Transform Infra-red spectroscopy). For this purpose a sample hydrogel was used and the results were noted using FTIR spectrometer (Varian, 640-IR Spectrometer made by Auatralia/USA). Since functional groups were same in the hydrogel samples, the FTIR photograph of NiPAAm-1 was interpreted.

The hydrogel systems were analyzed for their thermal degradation with a thermo-gravimetric analyzer (TA Instruments SDT Q. 600 V20.9 Build 20 simultaneous TGA-DSC). Heating rate adapted was $10^{o}$C/min until the maximum temperature, $600^{o}$C was established.

The morphology and porous structures of the dried and swollen hydrogels (pH = 8.0) were examined with scanning electron microscope (Hitachi 3700N) applying a voltage equal to 5.00 kV.

### Swelling Behavior

Swelling behavior of the synthesized so-polymeric systems were monitored by keeping the xerpgels into a specific volume of buffer solutions having varying pH values (1.0, 4.0, 5.5, 7.4 and 8.0) at $37^{o}$C. The disks were picked out of the solutions after regular intervals, blot dried and weighed (mt) for equilibrium swelling. For calculating swelling percentage (%S), following relationship was applied [16]:

$$\%S = m_t\text{-}m_o/m_o \times 100 \qquad (2.1)$$

Here, $m_o$ is the weight of the xerogel. Fick's model was applied to figure out mode of diffusion of the solution into the gel [17].

$$\ln (W_t/W_e) = \ln k + n \ln t \qquad (2.2)$$

Here, $W_t$ and $W_e$ are indicating the amount of the external medium diffused into the gel networks during dynamic and at equilibrium swelling state respectively, k represents the constant, whereas "n" is called diffusion exponent which describes the mechanism of water transport outside in the hydrogel network. Only the initial 60% swelling data was incorporated in the above equation for analysis.

The swelling kinetics can also be described by second order Schott's model [18,19] that equates as:

$t/ W_t = 1/ k_s W_e^2 + 1/W_e t$ (2.3)

## Drug loading

The synthesized xerogel disks were immersed in various drug solutions ($T_{NE1}$ (0.8 mg/ml), $T_{NE2}$ (1.6 mg/ml), $T_{NE3}$ (2.4 mg/ml), $T_{NE4}$ (3.2 mg/ml), $T_{NE5}$ (4.0 mg/ml) having EGDMA and $T_{ND1}$ (0.8 mg/ml), $T_{ND2}$ (1.6 mg/ml), $T_{ND3}$ (2.4 mg/ml), $T_{ND4}$ (3.2 mg/ml) containing DEGDMA) which were loaded with Tramadol HCl (model drug). The required pH i.e. 8.0 was maintained by phosphate buffer, whereas, the temperature was maintained at 37oC in a thermostat. For most reliable results, the drug was loaded by swelling the prepared disks in the buffer solution of optimum pH (8.0) to avoid any drug decomposition and undesired drug-polymer interaction, at increased temperatures during the polymerization process. At equilibrium of swelling, the drug loaded polymer disks were picked out of the drug solutions. The disks were dried under room conditions. Apparent milkiness in the drug loaded disks was taken as the indictor of sufficient amount of the active agent loaded in the hydrogels. Following equation [20] was used to calculate the estimated absorbency of Tramadol HCl by the hydrogels.

Absorbency $(Q) = (C_1V_1-C_2V_2)/m_o$ (2.4)

Here, $m_o$ is initial mass of the dried gel; Q (mg $g^{-1}$) is representing the absorbency of the active agent by the dried sample; $C_1$ (mg $ml^{-1}$) is the concentration of drug present initially in the loading solution having volume $V_1$ (ml); $C_2$ (mg $ml^{-1}$) is the amount of Tramdol HCl left behind after the gels have absorbed maximum amount of it and $V_2$ (ml) represents the volume of solution remained in the beaker after adsorption of the drug.

## Drug Release Studies of Hydrogels

Drug release behavior of the synthesized poly(NiPAAm-co-MA-co-AA) co-polymers was studied spectrophotometrically. For this purpose, the dried disks loaded with Tramadol HCl were introduced into the solution buffered at pH 8.0 keeping the temperature constant at 37oC, keeping the volume of the buffer solutions equal for all the samples. At fixed intervals, 3.0 ml of the buffer solution was collected from every sample to note their absorbance using UV-visible spectrophotometer preset at an optimum wavelength 240 nm. Calibration curve provided by the instrument was further used to convert absorbance determinations into concentration [21].

## Release kinetics

Experimental data was analyzed for the release studies of Tramadol HCl from the hydrogel disks using various equations zero order relationship [22], First order kinetic equation [23], Higuchi's equation [24] and Hixson-Crowell model [25], as given below:

Zero order kinetics:

$Q_t = k_o.t$ (2.5)

First order kinetics:

$n (100- Q_t) = \ln 100 - k_1 t$ (2.6)

Higuchi's equation:

$Q^t = k^H.t^{1/2}$ (2.7)

Hixson-Crowell model

$(100- Q^t)^{1/3} = 100^{1/3} - k_{HC}.t$ (2.8)

Where, $Q_t$ shows percentage of Tramadol HCl unloaded at time t; $k_o$, $k_1$, $k_H$ and $k_{HC}$ stands for release rate constants for zero order, 1st order, Higuchi and Hixcon-Crowell equation respectively. Moreover, Korsmeyer-Peppas model (eq. 2.9) was used to analyze the release mechanism in detail [26].

$$Q_t/Q_e=k_{KP}.t^n \qquad (2.9)$$

Here, $Q_t/Q_e$ is the fractional amount of the drug released at time t; the network structure and geometrical aspects of hydrogels can be were interpret by the constant $k_{KP}$ whereas the value of the release exponent "n" indicates Fickian or non-Fickian release mechanism of any drug. As prepared hydrogels systems were cylindrical (such as tablets), the initial 10 - 70% release data were used for analysis.

## Results and Discussion

### Synthesis and Characterization

The hydrogels were prepared through free radical polymerization. The nitrogen gas was bubbled to avoid any non-reliable interaction of oxygen with the reaction mixture. The slow heating rate was opted to make the smooth and uniform polymerization sure. Appearance of milkiness was taken as the phenomenon indicating the polymerization process successfully. The prepared hydrogel disks were avoided to dry in oven to prevent degradation of the gel. The washed and dried gel disks were preserved in air tight small containers separately.

The IR spectrum of selected NiPAAm hydrogel material (Figure 1) showed a peak at 3550 - 3450 $cm^{-1}$, typically indicating the vibration of hydrogen bonded –OH group [27]. The peak at 3000 - 2900 $cm^{-1}$ corresponding to –OH was probably due to acrylic acid dimmer, the peak at 1750 - 1700 $cm^{-1}$ (C=O stretching vibration) was considered because of ester linkage whereas the peak at 1650 - 1600 $cm^{-1}$ was representing the "C=O stretching vibration" experienced by acrylic acid content. A specific peak at 1700 - 1600 $cm^{-1}$ showed bond stretching of –(C=O)-NH-R, confirming the incorporation of N-isopropylacrylamide in the polymer network [27]. The peak near 1648 $cm^{-1}$ affirmed coil or helix formation inside the polymer network indicating the presences of cross-links [27]. The peaks at 1500 - 1400 $cm^{-1}$ because of asymmetric and symmetric vibrations, indicate carboxylate anions present in the structure.

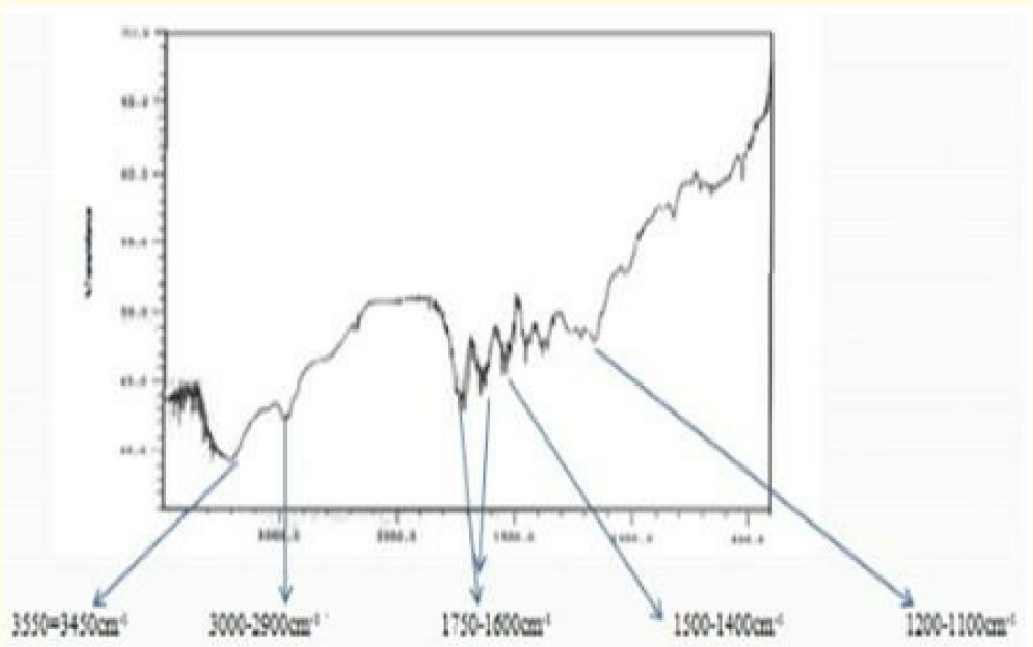



***Figure 1:*** *IR spectrum of optimized batch of NiPAAm-2 hydrogel cross-linked with DEGDMA.*

The thermal behavior of NiPAAm gels was analyzed using TGA (Figure 2a, 2b and 2c). The degradation of these polymers occurred in two phases. The first phase of degradation was observed at 250 - 400°C and the second phase at 450 - 600°C. Literature supports absence of significant degradation at temperatures lower than 250°C in homo-polymer p(NiPAAm)gels [28]. As discussed above, the presence of acrylic acid (hydrophilic component) not only caused an increase in LCST of the NiPAAm-1 and NiPAAm-2 gels from 32 to 33.6 and 33.3°C respectively, but also decreased the value of $T_g$ from 275°C to 40 and 45°C for both gels, respectively (Figure 2a, 2b, 2c). Our results are in coherence with previously reported Tg values for pure P (NiPAAm) gels which fell from 260°C to 45°C upon incorporation of acrylic acid and methacrylate [28]. Furthermore, the transition temperature (LCST) is adjustable (controlling the hydrophobic/hydrophilic balance of monomers and the polymer molecular weight) [29]. For example, enhanced the hydrophobic monomeric components (e.g. butyl methacrylate) resulted in decreased LCST [1]. However, the inclusive hydrophilic monomers foster the formation of hydrogen bondings within the structure thus increasing the LCST value for a particular gel system [30]. The co-polymers of NiPAAm and hydrophilic unities (in this particular case, acrylic acid) promoted LCST near to 37ºC i.e. the body temperature.

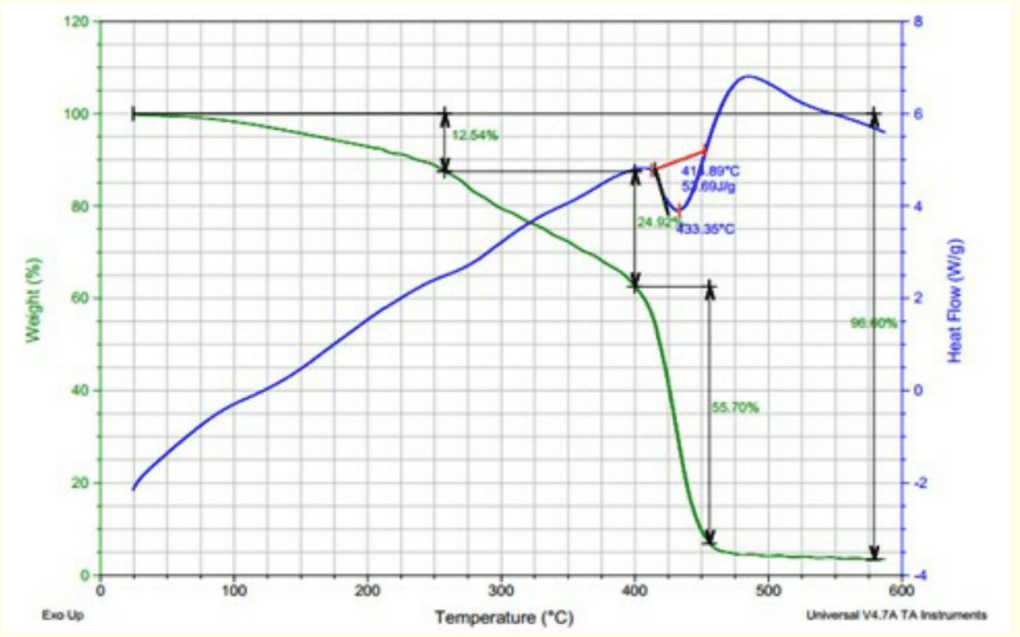



***Figure 2a:*** *DSC/TGA curves for optimized batch of NiPAAm-2 cross-linked with DEGDMA in dry state.*

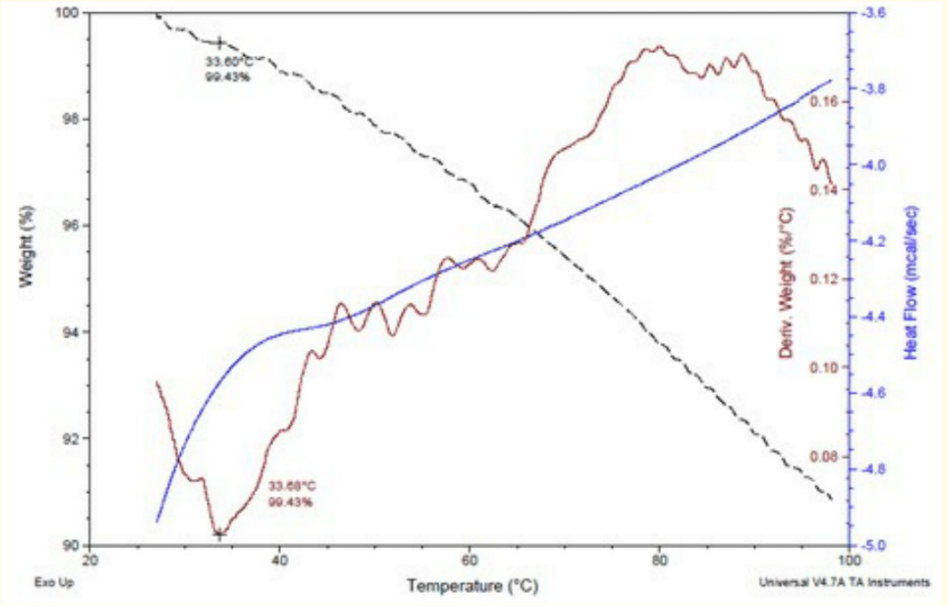



***Figure 2b:*** *DSC/TGA curves for optimized batch of poly (MA-co-AA-co-NiPAAm) cross-linked with EGDMA in equilibrium state at pH 8.0.*

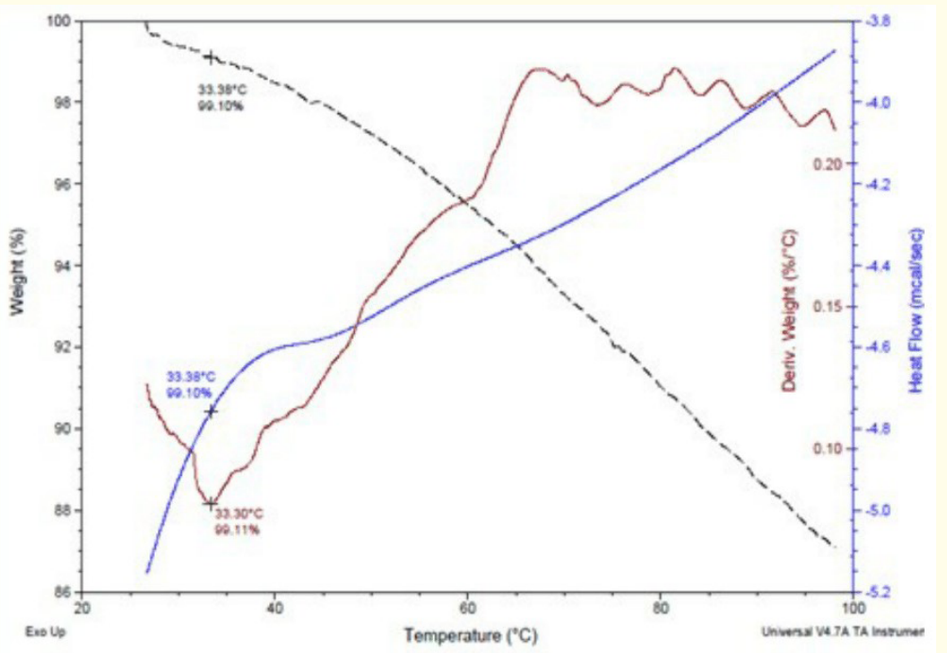



***Figure 2c:*** *DSC/TGA curves for poly (MA-co-AA-co-NiPAAm) cross-linked with DEGDMA in equilibrium state at pH 8.0.*

The morphology of the co-polymer hydrogel systems was studied by SEM as shown in figure 3a and 3b. Morphological comparison of the dry gel and the swollen hydrogel systems showed two differences in degree of porosity. It was observed that at equilibrium swelling, the chains relaxed allowing the penetration of medium into the gel networks. Moreover, the SEM photographs of the same hydrogel sample at pH 8.0 swollen up to its equilibrium stage seem to have more or less smooth surface owing to water retention within the porosite of the gel. The figure 3a clearly indicates that xerogel has uneven surface indicating the presence of pores of variable size in the ter-polymeric hydrogels. We can conclude that the pore size is not uniform inside the structure of the gel. The most probable reason may be the introduction of various moieties in the interior of the gel which were raised because of presence of three different monomers in composition of the hydrogels. Higher degree of freedom may allow the formation of cross-links at different distances thus creating a variety in size as well as shapes of the pores. Whatever the size and shape of the pore are, it is confirmed that the hydrogels present a porous structure capable of retaining and transferring fluids after swelling, which is to be expected since the porosity of the material yields a better swelling degree.


***Figure 3a:*** *SEM structures of the optimized batch [NiPAAm-1] inner surface in dry state.*

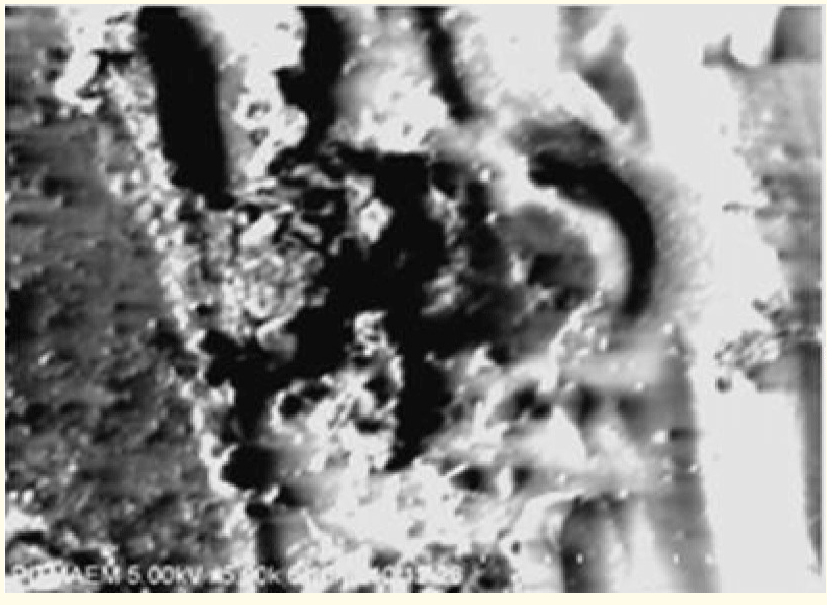


***Figure 3b:*** *SEM structures of the optimized batch [NiPAAm-2] inner surface in equilibrium state at pH 8.0.*

## Swelling Analysis

The dynamic and the equilibrium swelling were studied to interpret the influence of various pH of the external media and the nature of the chemical crosslinking agent. It was found that all the hydrogel samples showed accelerated dynamic ($m_t$-$m_o$/$m_o$) and equilibrium swelling ratio ($m_e$-$m_o$/$m_o$) in the basic media. This behavior of co-polymeric hydrogels may be attributed to its pH sensitivity. Being pH-sensitive polymers, their weak acidic groups attached to a non-polar backbone play a leading role in swelling behavior of the gels. The pendant acidic functional group added to the polymer backbone, releases hydrogel ions ($H^+$) in when an appropriate pH is provided to them thus changing the ionic strength in external media [31]. When ionization occurs, the dramatic extension of coiled chains takes place due to the electrostatic repulsions among similar charges thus controlling the swelling behavior. As the number ionizable acidic groups is the major controlling factor for the ionization concentration of these hydrogels so stronger electrostatic repulsions are experienced by negatively charged carboxylic groups on various polymer chains. Consequently, it increases the hydrophilic ability of hydrogels and higher swelling ratio is observed in basic medium (Figure 4a). Whereas, in acidic medium, especially when the pH of the medium is less than $pK_a$ of AA, the number of ionized carboxylic groups is not considerable and a reasonable number free carboxylic groups is present in the unionized form which results in the formation of H-bonded inter-polymeric complexes [32]. PHEMA (2-hydrogxymethylacrylate) based SPHs (super-porous hydrogels) synthesized by Omidian and his co-workers exhibited improved swelling upon incorporation of acrylic acid [33]. Similarly, Ranjha reported high swelling at basic pH (> 5.5) through chain relaxation in non-ionic vinylacetate (VAC), anionic acrylic acid (AA) or meth-acrylic acid (MAA) monomers and ethylene glycol dimethacrylate (EGDMA) [34].

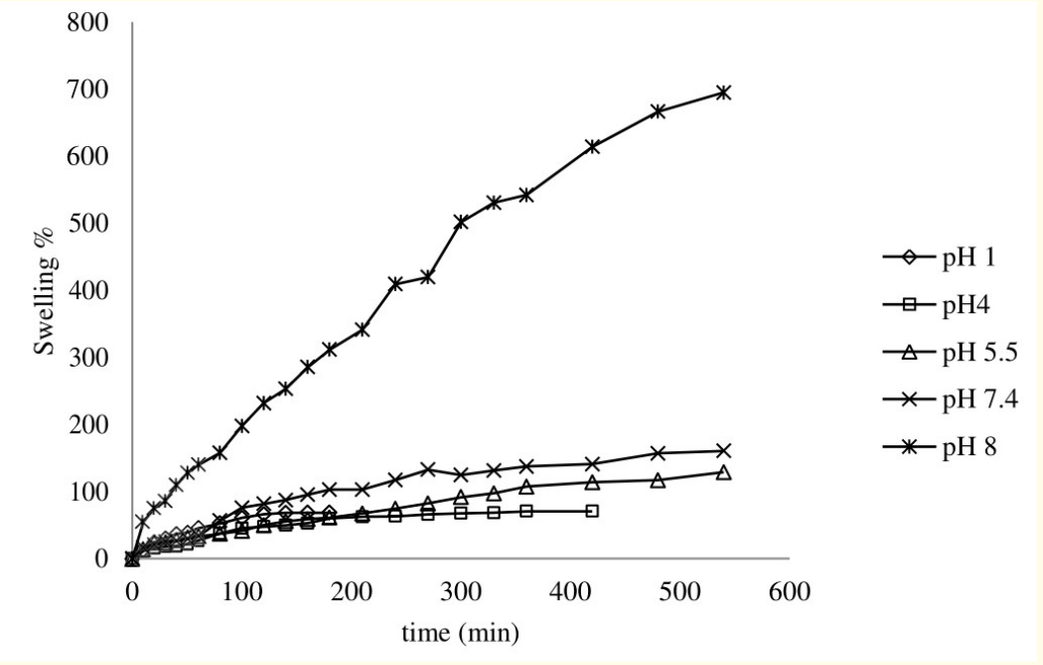



***Figure 4a:*** *Effect of pH on swelling percentage and equilibrium swelling of the poly (MA-co- NiPAAm-co-AA) cross-linked with DEGDMA.*

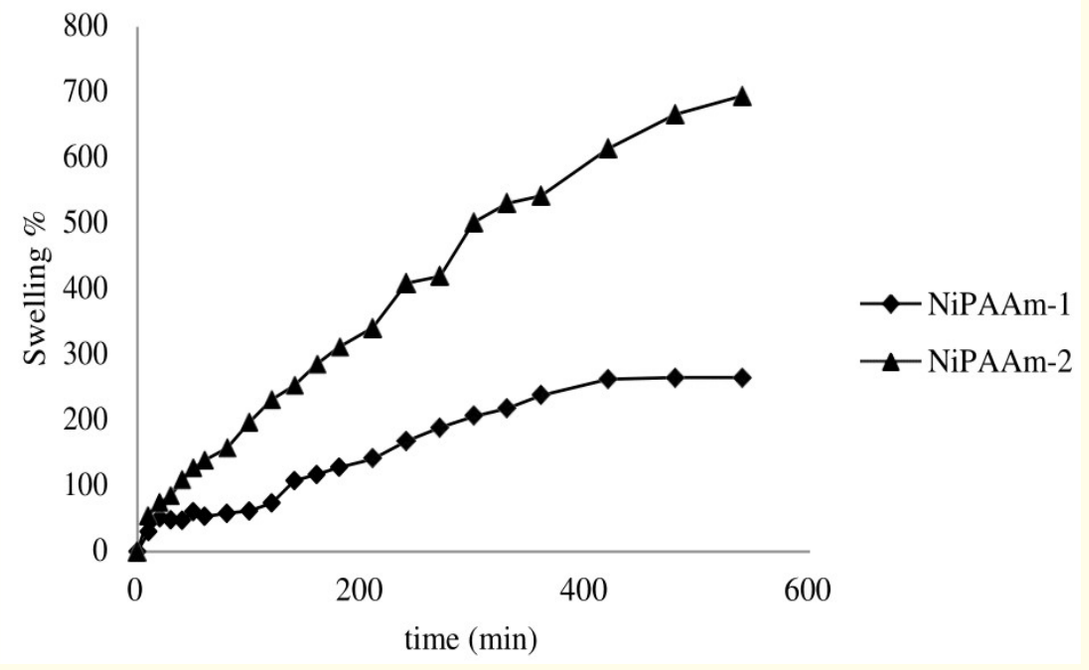



***Figure 4b:*** *Effect of nature of the cross linker on swelling percentage and equilibrium swelling of the poly (MA-co-NiPAAm-co-AA) hydrogels at pH 8.*

Anomalous swelling behavior in case of NiPPAm-1 hydrogels that underwent insignificant swelling in acidic media (Table 1) can be explained considering two factors. First, at acidic pH almost all free carboxylic groups, being unionized, may form hydrogen bonding with in the network structure. Secondly, the experimental temperature (37°C) is greater than that of LCST of the gels, so both of the factors combine together to inhibit the swelling of the gels at pH 1.0 and 4.0. However, NiPAAm-2 hydrogels exhibited a considerable swelling under acidic conditions.

| Sample | Media penetration velocity (mm/min×10-6) | Equilibrium media sorbed (mg media/mg polymer) | Schott's Model $R^2$ | Fick's Model | |
|---|---|---|---|---|---|
| | | | | n | $R^2$ |
| pH =1 | | | | | |
| NiPAAm-1 | ---- | ---- | ---- | ---- | ---- |
| NiPAAm-2 | 552.017 | 0.683168 | 0.960 | 0.690 | 0.974 |
| pH = 4 | | | | | |
| NiPAAm-1 | ---- | ---- | ---- | ---- | ---- |
| NiPAAm-2 | 637 | 0.703704 | 0.975 | 0.582 | 0.916 |
| pH = 5.5 | | | | | |
| NiPAAm-1 | 509.55 | 1.070922 | 0.980 | 0.577 | 0.757 |
| NiPAAm-2 | 806.79 | 1.2285816 | 0.902 | 0.505 | 0.979 |
| pH = 7.4 | | | | | |
| NiPAAm-1 | 637 | 1.304 | 0.985 | 0.862 | 0.967 |
| NiPAAm-2 | 1019 | 1.605405 | 0.972 | 0.712 | 0.911 |
| pH = 8 | | | | | |
| NiPAAm-1 | 2153 | 2.62122 | 0.898 | 0.535 | 0.789 |
| NiPAAm-2 | 4034 | 6.947977 | 0.854 | 0.642 | 0.983 |

***Table 1:*** *Summary of media penetration velocities, equilibrium media contents, Schott's model and power law parameters for the poly (MA-co-NiPAAm-co-AA) hydrogels.*

The rate of penetration in medium from the outside to the inside of the hydrogel disk was analyzed, determining media penetration velocity (ν), using the following equation,

$$\nu = 1/2\rho A.\delta w/\delta t \quad (3.1)$$

Here, "ρ" stands for density of medium; A represents area of the one face of the particular disk; w stands for mass of the polymer at time t. Initial time data (less than 15 minutes) was selected to determine the media penetration velocity (Table 1). As published earlier, a rubbery region is produced when the polymer swells on media penetration through the glassy polymer [32]. As expected from the preliminary characterization, the DEGDMA cross-linked gels showed higher media penetration velocity than that of the hydrogel samples having EGDMA (Figure 5a). The equilibrium media content was observed to be directly changed with the media penetration velocity for hydrogels cross-linked with different cross-linkers at all the pH values as shown in the representative plot for NiPAAm-2 sample having DEGDMA as the cross-linking agent (Figure 5b). The similar trend has also been reported in poly (NIPA-co-FOSA) copolymers [35]. The direct variability of equilibrium media content with the media penetration velocity suggests that the media penetration velocity may be helpful for the prediction of the equilibrium media content in initial experimental timings such that in minutes rather than in hours and days.

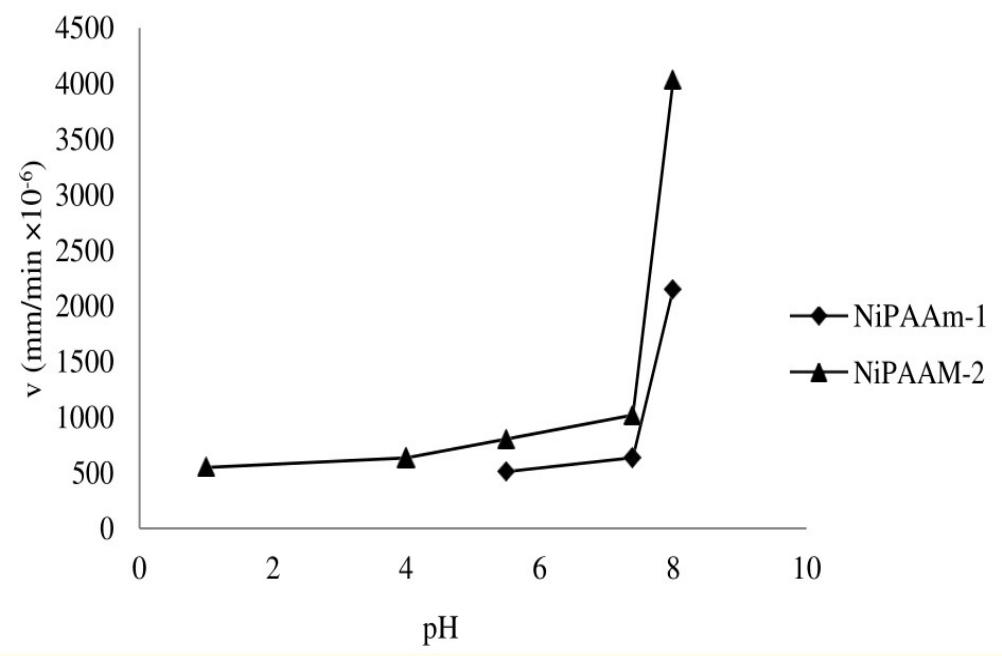



***Figure 5a:*** *Media penetration velocity at pH 1-8 in NiPAAm hydrogels.*

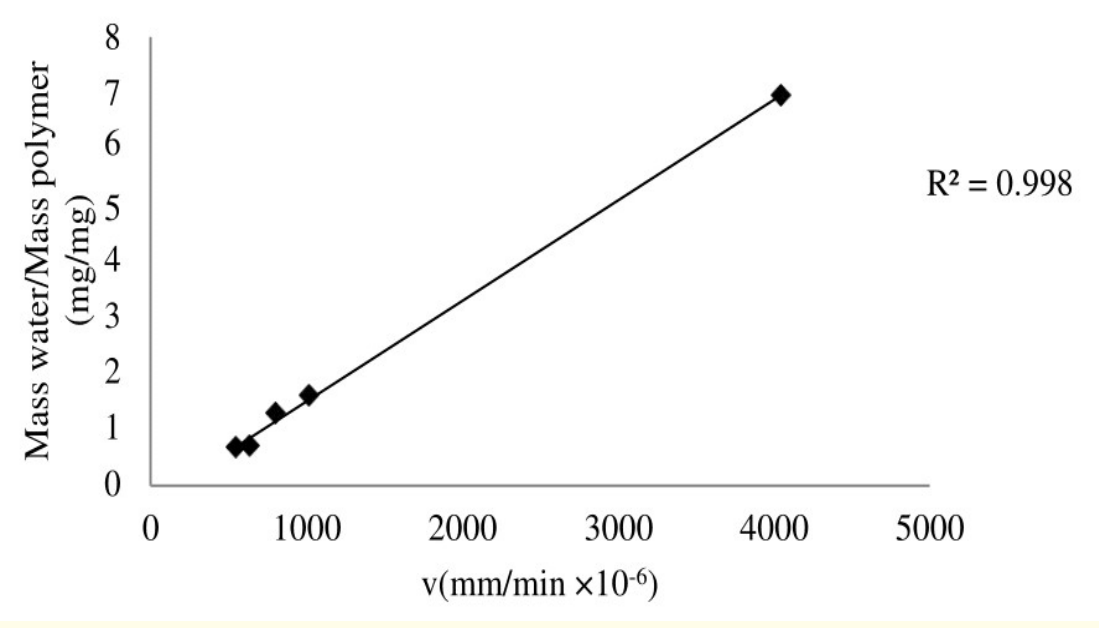



***Figure 5b:*** *Equilibrium media content at pH 1-8 as a function of media penetration velocity in the sample NiPAAm-2.*

The kinetic order of swelling for all these hydrogels was determined using 1st order model (Fick's model i.e. Maxwell-Peppas model) and second order model (Schott's model). It is also likely, that swelling of hydrogels at a certain time may follow both of these kinetic orders [36]. The diffusion exponent calculated from Maxwell-Peppas model was used to interpret the mechanism of the media sorption (Table 1) [37]. In our studies, the Fick's law was applied for the first swelling times; because for longer times, there was a deviation in this behavior. So the swelling fraction values ($W_t/W_e$) less than or equal to 0.6 were established in accordance with bibliographic data [38]. On the other hand, the Schott's model was applied for longer times when the density of the sample has been increased. In the present studies, NiPAAm-1 hydrogels did not exhibit a reasonable swelling in acidic medium as discussed earlier, and showed preference for Schott's model in basic medium. NiPAAm-2 co-polymeric hydrogels exhibited an alternative model fit with the pH change from 1.0 to 8.0. It can be assumed that as the LCST for these polymers were found to be not more than 33.6°C, so these should be shrunk at 37°C, the experimental temperature, especially in acidic medium where no support for swelling is provided by acrylic acid. So at most of reaction conditions, NiPAAm co-polymeric hydrogels showed best fit with Schott's model, indicating the chain relaxations in longer time on one hand and non- Fickian swelling mechanism on the other side. Fickian behavior for various hydrogels under similar conditions has been reported by many authors [39-41].

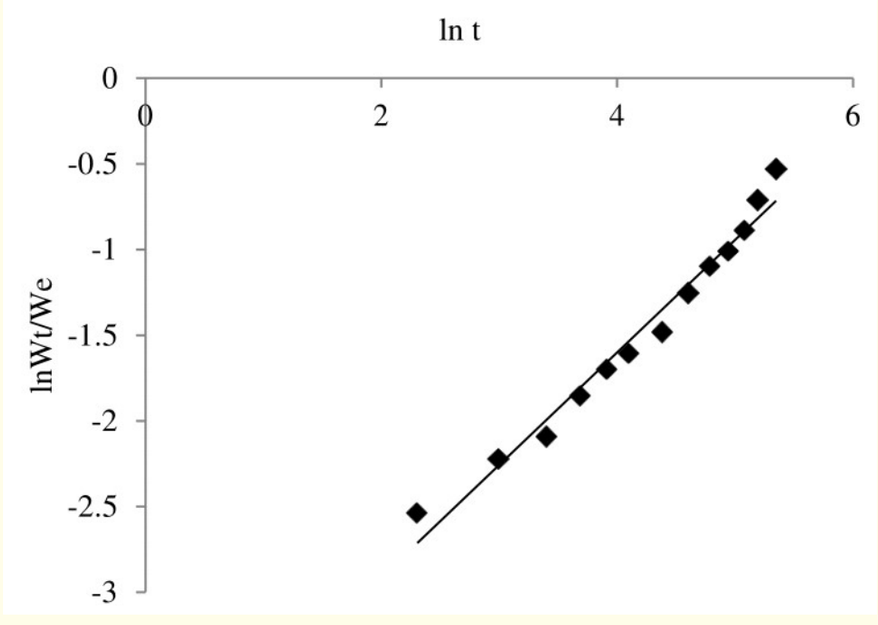



***Figure 6:*** *Graphic of Maxwell-Peppas Model at pH 8 for the hydrogel sample NiPAAm-2.*

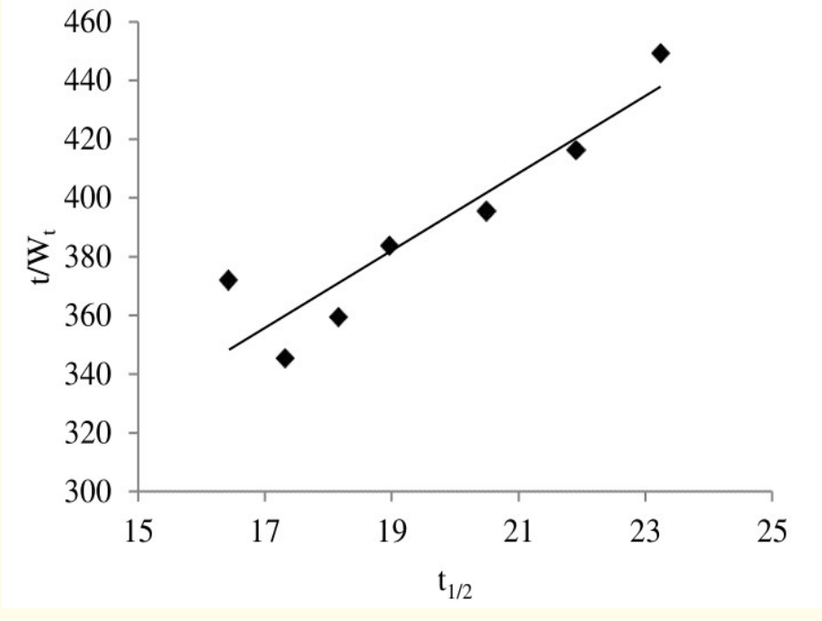



***Figure 7:*** *Graphic of Schott"s model at pH 8 for the hydrogel sample NiPAAm-2.*

## Network Parameters

When a cross-linked polymer is placed in a suitable solvent, instead of complete dissolution, it will preferably swell by absorbing only a particular amount of the solvent. To characterize polymers, swelling is less complicated and easy to handle phenomenon. That is why; the equilibrium swelling values of these hydrogels were applied to estimate the effectiveness of the cross-linking agent and pH, major factors affecting swelling in these gels, on their network parameters. Flory-Rehner model was applied to find out $M_c$ (molecular weight between the cross links) which is considered very important parameter characterizing the cross linked parameters:

$$M_c = -d_p V_s / (v_{2,s}^{1/3} - v_{2,s}/2) [\ln (1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2] \quad (3.2)$$

Whereas, the following equation was applied to determine volume fraction

$$v^{2,s} v^{2,s} = [1 + d_p/d_s (W_a/W_b - 1)]^{-1} \quad (3.3)$$

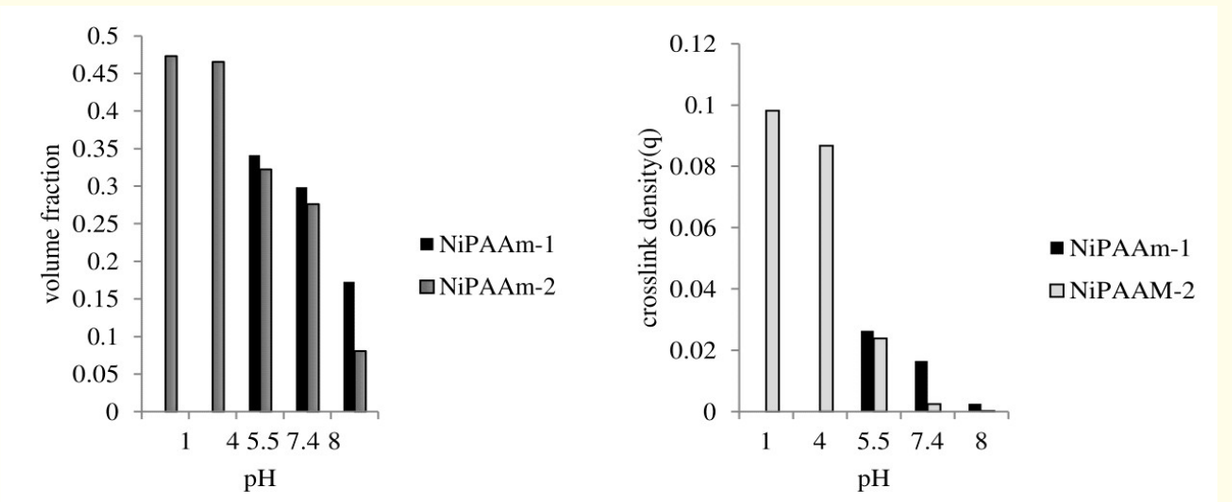
Here, $d_p$ and $d_s$ (1g/ml) indicate densities of co-polymer and respectively. Density of hydrogels was measured by "solvent displacement method" taking n-hexane as a non-solvent. $M_b$ and $M_a$ stand for the masses of dry gel samples and fully equilibrated samples of hydrogels. Moreover, $V_s$ represents molar volume of the water (18.0 ml/mol) whereas χ is Flory-Huggins parameter representing polymer-solvent interaction. To study the effect of pH on network parameters, equilibrium swelling results of the synthesized hydrogels were incorporated to calculate $M_c$ in various buffer solutions ranging from pH=1.0 to pH= 8.0, at 37°C. Experimental values of Mc and other related parameters have been compiled in the table 2.

| Sample | Cross linking ratio ($10^2$) | Volume fraction ($V_{2,s}$) | Molecular weight ($M_c$) | Cross link density (q) | Mesh size (ξ) |
|---|---|---|---|---|---|
| pH =1 | | | | | |
| NiPAAm-1 | 3.84 | ----- | ----- | ----- | ----- |
| NiPAAm-2 | 3.73 | 0.4732 | 970 | 0.0928 | 23.78 |
| pH =4 | | | | | |
| NiPAAm-1 | 3.84 | ----- | ----- | ----- | ----- |
| iPAAm-2 | 3.73 | 0.4658 | 1027 | 0.0876 | 24.6 |
| pH =5.5 | | | | | |
| NiPAAm-1 | 3.84 | 0.3415 | 3411 | 0.0264 | 51.88 |
| NiPAAm-2 | 63.73 | 0.3226 | 3764 | 0.0239 | 53.51 |
| pH =7.4 | | | | | |
| NiPAAm-1 | 3.84 | 0.2989 | 5413 | 0.0166 | 65.45 |
| NiPAAm-2 | 3.73 | 0.2765 | 36312 | 0.0025 | 174 |
| pH =8 | | | | | |
| NiPAAm-1 | 3.84 | 0.1732 | 34578 | 0.0026 | 198 |
| NiPAAm-2 | 3.73 | 0.0811 | 356096 | 0.00025 | 820 |

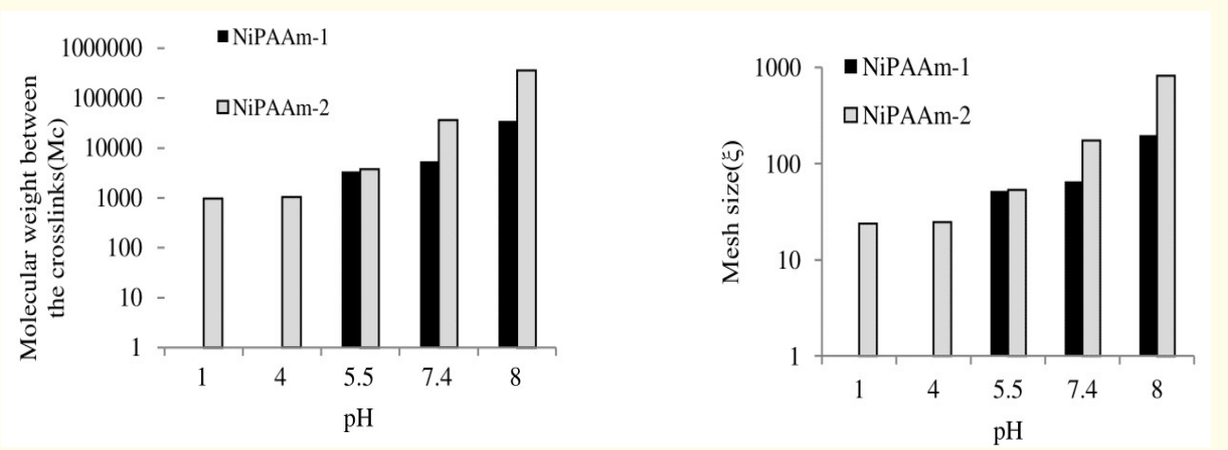
***Table 2:*** *Network parameters determined from equilibrium swelling studies for the NiPAAm hydrogels in various pH media at 37°C.*

It is clear from the tables 2 that Mc value increased with increasing cross-linking ratio and volume fraction. Moreover, effect of nature of cross-linker was also estimated and it was found that Mc value was higher in the hydrogels cross-linked with DEGDMA introducing higher cross- linking ratio as compared to that of EGDMA as shown in the figure 8b. Additionally, the figures 8a, 8b, 8c and 8d are displaying the effect of pH on the network parameters. It was found that the pH affected the Mc directly and remarkably. For example, it

approached to 356096 g/mol from 970 g/mol, for NiPAAm-2 and for NiPAAm-1, from 3411 g/mol to 34578 g/mol while changing the pH of the external media from 1.0 to 8.0. The observation may be attributed to enhanced ionization of the –COOH groups present in the network structure due to shifting of pH to produce charged carboxylate, $–COO^-$, groups and $H_3O^+$ counter ions inside polymeric network structure. A high osmotic pressure is resulted because of neutralization of static charges present on the polymer chains by interaction of free counter ions inside the gel network structure, thus introducing enhanced swelling percentage. Moreover, carboxylate groups experience electrostatic repulsive force, which are responsible for the relaxation of the polymer network.




**(8a)** **(8b)**




**(8c)** **(8d)**

***Figure 8:*** *Effect of nature of cross linker on various network parameters.*

***Figure 8a:*** *Plot between volume fraction and pH.*

***Figure 8b:*** *Plot between crosslink density and pH.*

***Figure 8c:*** *Plot between Molecular weight between the crosslinks and pH.*

***Figure 8d:*** *Plot between the mesh size and pH.*

Characterizing cross-linked polymers, is another significant parameter called cross-linking density, q

$q = M_r/M_c$ (3.4)

$M_r$ (molar mass of the repeat unit) was calculated by following equation:

$$M_r = m_{NiPAAm} M_{NiPAAm} + m_{MA} M_{MA} + m_{AA} M_{AA} / m_{NiPAAm} + m_{MA} + m_{AA} \quad (3.5)$$

Here $m_{NiPAAm}$, $m_{AA}$ and $m_{MA}$ stand for masses of NiPAAm, AA and MA; whereas, $M_{NiPAAm}$, $M_{MA}$ and $M_{AA}$ are the molar masses of NiPAAm, MA and AA respectively.

Mesh size, ξ, describing the empty space available to facilitate solute mobility within the hydrogel network, is a frequently applied parameter for analysis of cross linked polymers. Mesh size was calculated using as given below:

$$\xi = v_{2,s}^{-1/3} (2M_c/M_r)^{1/2} Cn^{1/2} l \qquad (3.6)$$

Where, $M_r$ represents the molecular weight of repeat unit, l, is the bond length (for C-C =1.54 Å) and $C_n$, stands for the characteristic ratio (taken 6.7 for AA [42]). The mesh size (ξ) and crosslink density (q) values for these hydrogel systems are represented in table 2. The values of ξ increased from 23.78 to 820 Å as the swelling of hydrogels increased with the medium pH.

## Drug Release Kinetics

After optimizing the conditions, the pH 8.0 was taken as the medium where maximum swelling was exhibited by all hydrogel systems so the selected drug Tramadol HCl was loaded and released at pH 8.0. Increase in the initial concentration of the drug, results in more amount of drug to be loaded in the polymeric network as indicated in figure 9. This can be explained in terms of greater concentration gradient in the loading solution. Again, the figure 9 is showing the comparative absorbency of the drug depending upon the cross-linking agent. It is clear that the absorbency of co-polymeric hydrogels cross-linked with DEGDMA is higher than those having EGDMA as the cross-linking agent. It is due to the greater swelling ability of DEGDMA, as already discussed in the previous sections.

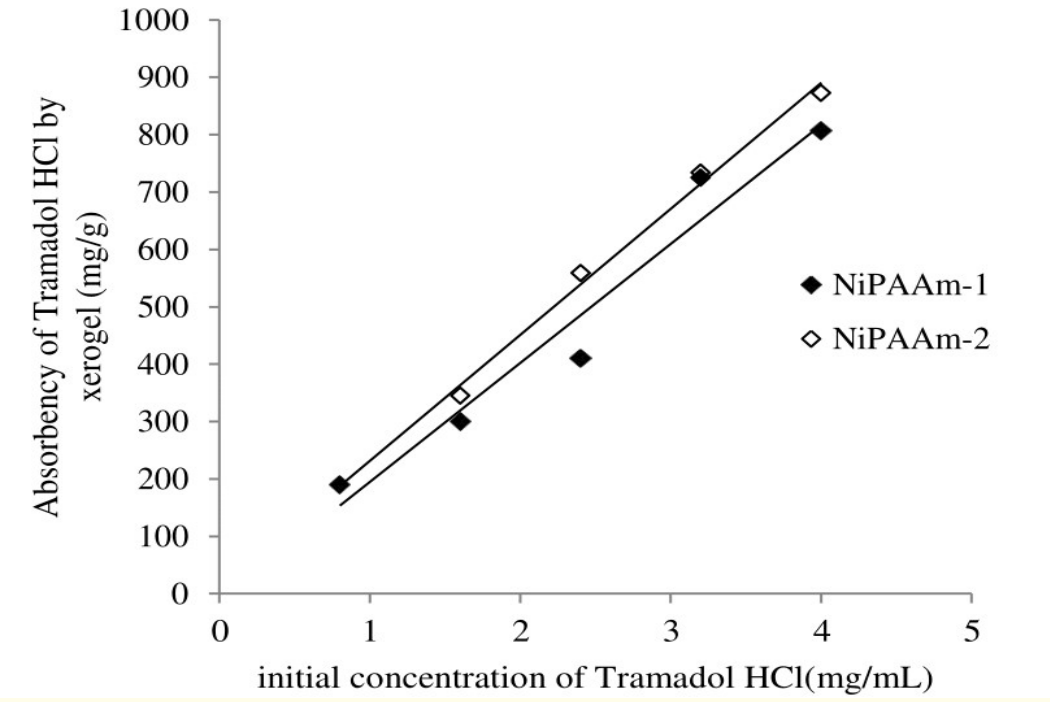



***Figure 9:*** *Absorbency of Tramadol HCl with various initial concentrations of the drug.*

As it is reported that the degree of cross linking and initial concentration of the chemical agent loaded in the hydrogel system are the key factors affecting the release behavior [43], so the release analysis was carried out for these parameters only. In the figure 10 representing the release profiles for NiPAAm-1 hydrogels, no remarkable effect was observed at initial stages. The difference in the drug release rate for various initial concentrations of the Tramadol HCl was negligible during first 30 minutes of exposure of the drug loaded disks into the buffer solution at pH 8.0. However, with passage of swelling time, the difference between the curves is becoming more and more prominent especially when the systems with higher drug concentrations were used; it was observed that the quantity and rate of

release of the Tramadol HCl were increased. The major reason for the fact might be a prominent concentration gradient responsible for an active transportation of the active agent through hydrogel network. conclusively, variation in drug loading concentration is a real tool for controlling the drug release [44]. The effect of nature of the cross-linker on rate of drug release is shown in figure 11. The release rate is faster in the gels cross-linked with DEGDMA, than those cross-linked with EGDMA. However, the difference is more pronounced in the NiPAAm gels being loaded with the higher initial drug concentration.

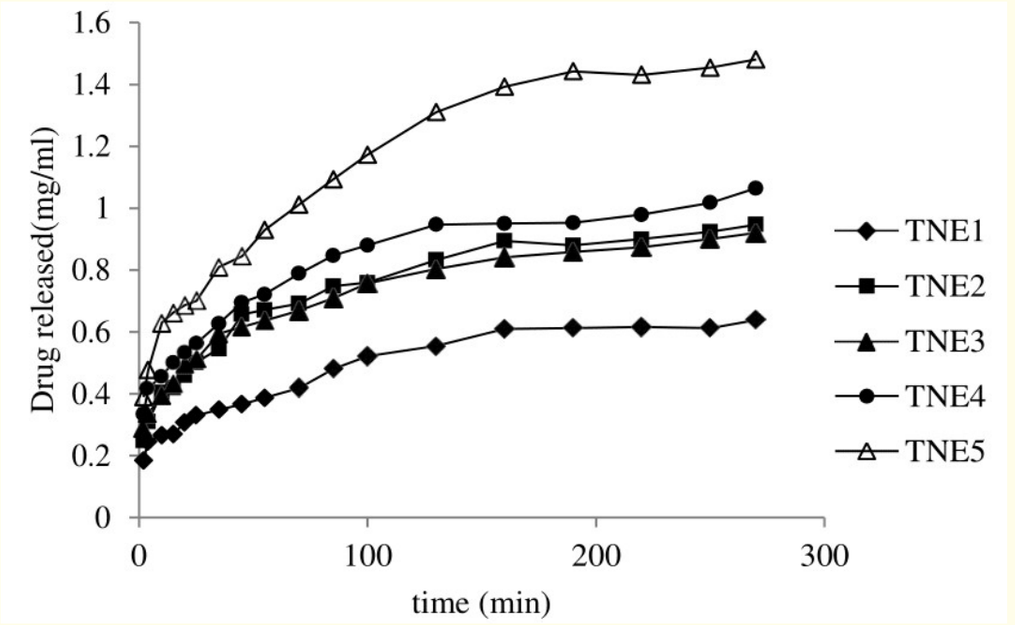



***Figure 10:*** *Influence of amount of Tramdol HCl in the matrix on the release rate for the hydrogel NiPAAm-1 at pH 8.0.*

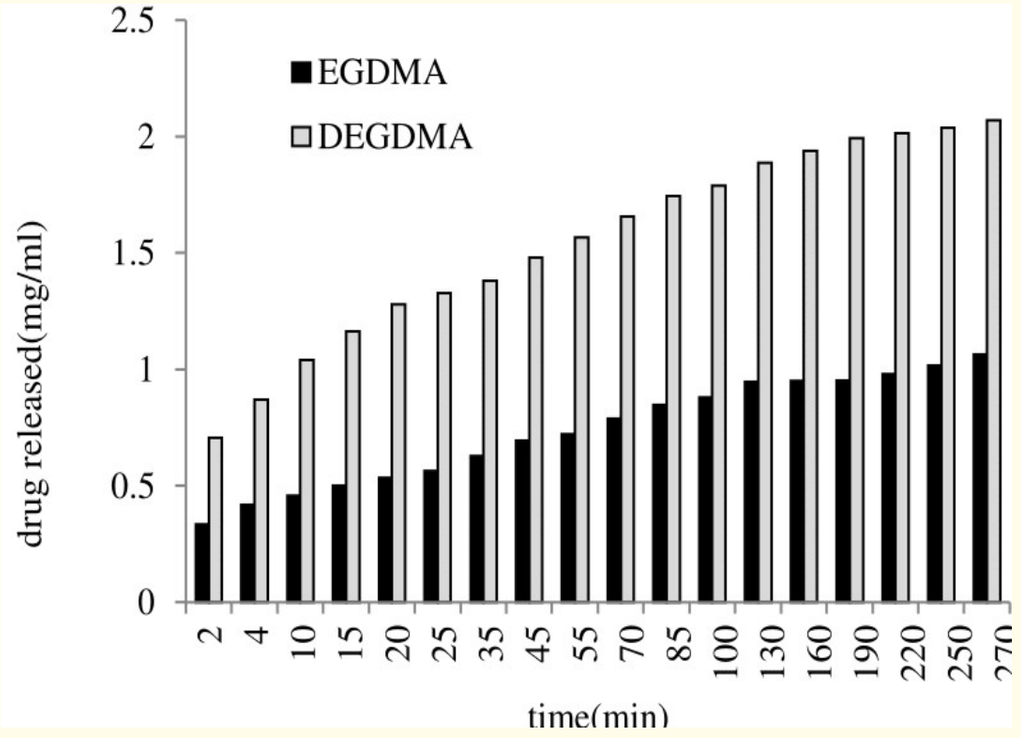



***Figure 11:*** *Effect of nature of the cross-linker on release rate of Tramadol HCl in NiPAAm gels.*

Different equations have been suggested to modulate the release kinetics of hydrogels. When the drug release rate is not depending on the initial concentration of the active agent, the system is said to follow the zero order kinetics [22]. Whereas, dependency of release rate on the initial concentration of the drug is studied as the first order kinetics [23]. Higuchi model goes side by side with the Fickian diffusion [24]. The effect of changing surface area and size (diameter) of the hydrogel particles or disks on the release behavior of formulations can be studied applying Hixson-Crowell cube root law [25].

For a more precise description of the release mechanism, Korsmeyer-Peppas power law was applied to initial 60% release data. The most suitable model was taken according to the best correlation factor value for explaining drug release behavior of hydrogel systems. The results found are tabulated in the table 3. In general, all the formulations followed the first order kinetics, owing to better correlation coefficient values as compared to those for the zero order kinetic models fit. Conclusively, it is proposed that these hydrogel systems exhibited and limited drug concentration dependency. Moreover, almost all the samples followed the Higuchi model. The correlation factor values and other concerned parameters are tabulated in the tables 3.

| Sample | Zero-order | | First-order | | Higuchi | | Hixson-Crowell | | Korsmeyer-Peppas | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ko (%min$^{-1}$) | $R^2$ | $k_1$ (min$^{-1}$) | $R^2$ | $k_H$ (%min$^{-1/2}$) | $R^2$ | $k_{HC}$ (%min$^{-1}$) | $R^2$ | n | $R^2$ | $k_{KP}$ (%min$^{-n}$) |
| TNE1 | 0.245 | 0.879 | 0.012 | 0.961 | 5.213 | 0.932 | 0.011 | 0.944 | 0.200 | 0.931 | 0.265 |
| TNE2 | 0.240 | 0.815 | 0.012 | 0.980 | 7.340 | 0.977 | 0.020 | 0.971 | 0.265 | 0.992 | 0.223 |
| TNE3 | 0.226 | 0.838 | 0.012 | 0.990 | 6.536 | 0.986 | 0.018 | 0.955 | 0.220 | 0.980 | 0.267 |
| TNE4 | 0.221 | 0.832 | 0.010 | 0.971 | 5.809 | 0.986 | 0.016 | 0.978 | 0.199 | 0.970 | 0.280 |
| TNE5 | 0.259 | 0.877 | 0.015 | 0.978 | 5.588 | 0.979 | 0.013 | 0.958 | 0.240 | 0.982 | 0.230 |
| TND1 | 0.205 | 0.800 | 0.010 | 0.951 | 6.693 | 0.944 | 0.018 | 0.897 | 0.290 | 0.972 | 0.237 |
| TND2 | 0.134 | 0.718 | 0.012 | 0.948 | 7.181 | 0.972 | 0.034 | 0.951 | 0.150 | 0.985 | 0.467 |
| TND3 | 0.207 | 0.811 | 0.014 | 0.984 | 6.424 | 0.941 | 0.019 | 0.879 | 0.234 | 0.995 | 0.294 |
| TND4 | 0.202 | 0.781 | 0.014 | 0.995 | 6.887 | 0.966 | 0.021 | 0.915 | 0.246 | 0.993 | 0.291 |

***Table 3:*** *Kinetic parameters of Tramadol HCl release from the matrix tablets of NiPAAm gels.*

Corresponding to the Higuchi model fit, all NiPAAm gels showed Fickian behavior having n=0.199 to 0.265 for NiPAAm-1 and 0.155 to 0.290 for NiPAAm-2. The drug release mechanism was quite opposite to that exhibited during swelling by NiPAAm gels, where they showed non-Fickian behavior as shown in the table 1. This dramatic change undergone by the NiPAAm gels may be explained on the basis of presence of dual-sensitivity in the gels towards temperature and pH, and also there may be some strong interaction between the drug particles and the polymer network. In fact all the NiPAAm hydrogels samples were collapsed during first 10 minutes of their exposure to the buffer solution. The initial uptake of water due to diffusion developed some type of strong interaction with the drug, resulting greater osmotic pressure to cause the burst release of the drug; ca. 40% of the drug was released during first 15 minutes due to the collapse of the hydrogel disks providing greater surface area. That is the reason that NiPAAm gels followed Higuchi model along with Fickian release mechanism.

## Conclusion

It is concluded that the swelling behavior and hydrolytic outcomes of the formulations depend on the nature of the chemical cross linkers and the pH of the release medium. These hydrogels showed a volume phase transition temperature greater than 32oC (the LCST of PNiPAAm). It was found that the hydrophilic component AA shifted the LCST to the higher temperature and the hydrophobic components such as MA, DEGDMA and EGDMA have provided a necessary mechanical strength to resist against the peristaltic movement of the stomach. Following the first order kinetics, the release of Tramadol HCl from Poly (NiPAAm-co-MA-co-AA) hydrogels is strongly influenced by the copolymer composition and the initial concentration of the drug. Controlling the initial concentration of Tramadol HCl loaded in the polymer network structure allows tuning of the release rate of the Tramadol HCl.

In short, the enriched NiAAm hydrogel disks avoid the release of the active agent in stomach, facilitating the drug release in proximal part of gastrointestinal tract. The findings suggest that the designed NiPAAm hydrogels are exhibiting a promising trend for use as pH-modulated drug release systems.

## Bibliography

1. Jeong B., *et al*. "Thermosensitive sol-gel reversible hydrogels". *Advanced Drug Delivery Reviews* 54.1 (2002): 37-51.
2. Chen GH and Hoffman AS. "Graft co-polymers that exhibit temperature-induced phase transitions over a wide range of pH". *Nature* 373.6509 (1995): 49-52.
3. Yoshida R., *et al*. "Comb-type grafted hydrogels with rapid de-swelling response to temperature change". *Nature* 374 (1995): 240-242.
4. Kwon IC., *et al*. "Electrically credible polymer gels for controlled release of drugs". *Nature* 354 (1991): 291-293.
5. Brazel CS and Peppas NA. "Synthesis and characterization of thermo and chemomechanically responsive poly [(N-isopropylacrylamide)-co-(methacrylic acid)] hydrogels". *Macromolecules* 28.24 (1995): 8016-8020.
6. Bae YH., *et al*. "Thermo-sensitive polymers as on-off switches for drug release". *Macromolecular Rapid Communications* 8.10 (1987): 481-481.
7. Gutowska A., *et al*. "Thermosensitive interpenetrating polymer networks-synthesis, characterization and macromolecular release". *Macromolecules* 27.15 (1994): 4167-4175.
8. Pham AT and Lee PI. "Probing the mechanism of drug release from hydroxylpropyl methy cellulose (hpmc) matrices". *Pharmaceutical Research* 11.10 (1994): 1379-1384.
9. Moechel JE and Lippold BC. "Zero-order drug release from hydrocolloid matrixes". *Pharmaceutical Research* 10.7 (1993): 1066-1070.
10. Colombo P., *et al*. "Drug diffusion front movement is important in drug release control from swellable matrix tablets". *Journal of Pharmaceutical Sciences* 84.8 (1995): 991-997.
11. Han H., *et al*. "Doxorubicin-encapsulated thermo-sensitive liposomes modified with poly (n-isopropyleacrylamide-co-acrylamide): Drug release behavior and stability in the presence of serum". *European Journal of Pharmaceutics and Biopharmaceutics* 62.1 (2006): 110-116.
12. Akdemir Z and Kayaman-Apohan N. "Investigation of swelling, drug release and diffusion behaviors of poly (n-isopropylacrylamide)/poly (n-vinylpyrrolidone) full-IPN hydrogels". *Polymers for Advanced Technologies* 18.11 (2007): 932-939.
13. Oliveira D., *et al*. "Contributions to the thermodynamics of polymer hydrogel systems". *Polymer* 45.4 (2004): 1287-1293.

14. Yildiz B., *et al*. "Synthesis and characterization of thermo-responsive isopropylacrylamide- acrylamide hydrogels". *European Polymer* 38.7 (2002): 1343-1347.

15. Lehmann KA. "Tramadol in acute pain". *Drug* 53.2 (1997): 25-33.

16. Zafar., *et al*. "Synthesis and swelling kinetics of a cross-linked ph-sensitive ternary co- polymer gel system". *Polymer Korea* 32.3 (2008): 219-229.

17. Malana M and Zohra R. "The release behavior and kinetic evaluation of tramadol hcl from chemically cross linked co-polymeric hydrogels". *DARU Journal of Pharmaceutical Sciences* 21.1 (2013): 1-10.

18. Lee JW., *et al*. "Synthesis and characteristics of interpenetrating polymer network hydrogel composed of chitosan and poly(acrylic acid)". *Journal of Applied Polymer Science* 73.1 (1999): 113-120.

19. Schott H J. "Swelling kinetics of polymers". *Journal of Macromolecular Science, Part B* 31.1 (1992): 1-9.

20. Xinming L and Yingde CUI. "Study on synthesis and chloramphenicol release of poly (2- hydroxymethylmethacrylate-co-acrylamide) hydrogels". *Chinese Journal of Chemical Engineering* 16.4 (2008): 640- 645.

21. Gomez ML., *et al*. "Influence of the ionic character of the drug on its release rate from hydrogels based on 2-hydroxymethylmethacrylate and acrylamide synthesized by photo polymerization". *eXPRESS Polymer Letters* 6.3 (2012): 189-197.

22. Najib N andSuleiman M. "The kinetics of drug release from ethyl cellulose solid dispersions". *Drug Development and Industrial Pharmacy* 11.12 (1985): 2169-2181.

23. Desai SJ., *et al*. "Investigation of factors influencing release of solid drug dispersed in wax matrices iii. Quantitative studies involving polyethylene plastic matrices". *Journal of Pharmaceutical Sciences* (1966): 1230-1234.

24. Higuchi T. "Mechanism of sustained action medication. Theoretical analysis of rate of solid drugs dispersed in solid matrices". *Journal of Pharmaceutical Sciences* 52.12 (1963): 1145-1149.

25. Hixson AW and Crowell JH. "Dependence of reaction velocity upon surface and agitation". *Industrial and Engineering Chemistry* 23.8 (1931): 923-931.

26. Korsmeyer RW., *et al*. "Mechanism of solute release from porous hydrophilic polymers". *Indian Journal of Pharmaceutical Sciences* 15.1 (1983): 25-35.

27. Pal K., *et al*. "Effect of heat treatment of starch on the properties of the starch hydrogels". *Materials Letters* 62.2 (2008): 215-218.

28. Kim B., *et al*. "Dynamic swelling behavior of ph-sensitive anionic hydrogels used for protein delivery". *Journal of Applied Polymer Science* 89.6 (2003): 1606-1613.

29. Ruel-Gariépy E and Leroux J. "In situ forming hydrogels- review of temperature-sensitive systems". *European Journal of Pharmaceutics and Biopharmaceutics* 58.2 (2004): 409-426.

30. Kim S., *et al*. "Engineered polymers for advanced drug delivery". *European Journal of Pharmaceutics and Biopharmaceutics* 71.3 (2009): 420-430.

31. Langer R and Peppas N A. "Advances in biomaterials, drug delivery and bionanotechnology". *AIChE Journal* 49.12 (2003): 2990-3006.

32. Khutoryanskiy VV., *et al*. "Ph effects in complex formation and blending of poly (acrylic acid) with poly (ethylene oxide)". *Langmuir* 20.9 (2004): 3785-3790.

33. Omidian H., *et al*. "Swelling and mechanical properties of modified hema-based super-porous hydrogels". *Journal of Bioactive and Compatible Polymers* 25.5 (2010): 483-497.

34. Ranjha NM. "Swelling behavior of pH-sensitive cross-linked poly (vinylacetate-co-acrylic acid) hydrogels for site specific drug delivery". *Pakistan Journal of Pharmaceutical Sciences* 12 (1999): 33-41.

35. Tia Q., *et al*. "Hydrophobic association and temperature and ph sensitivity of hydrophobically modified poly (n-isopropylacrylamide-co-acrylamide) gels". *Journal of Applied Polymer Science* 87.14 (2003): 2406-2413.

36. Mullerney MP. "Drug diffusion in hydrophobically modified N, N-dimethylacrylamide hydrogels". *Polymer* 47.11 (2006): 3845-3855.

37. Jabbari E and Nozari S. "Strain induced clustering in polyelectrolyte hydrogels". *European Polymer Journal* 36 (2008): 2685-2692.

38. Hiratani H., *et al*. "Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities". *Macromolecular Bioscience* 5.8 (2005): 728-733.

39. Liu Q., *et al*. "Mass transport through swelling membranes". *International Journal of Engineering Science* 43.19-20 (2005): 1464-1470.

40. Vrentas JS and Vrentas CM. "Steady viscoelastic diffusion". *Journal of Applied Polymer Science* 88.14 (2003): 3256- 3263.

41. Afif AE and Grame M. "Non-Fickin transport in polymers". *Journal of Rheology* 46.3 (2002): 591-628.

42. Gudeman LF and Peppas NA. "pH-sensitive membranes from poly (vinyl alcohol)/poly (acrylic acid) interpenetrating networks". *Journal of Membrane Science* 107.3 (1995): 239-248.

43. Landner WD., *et al*. "Controlled release of drugs from hydrocolloid embedding". *Pharmazei* 51 (1996): 263-272.

44. Dimitrov M., *et al*. "Hydrogels based on chemically crosslinked polyacrylic acid: biopharmaceutical chacterization". *Acta Pharmaceutica* 53.1 (2003): 25-31.

**Volume 5 Issue 2 February 2018**