ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE ENGINEERING AND TECHNOLOGY

MODIFIED HYDROGELS BASED on *N,N*-DIMETHYLAMINOETHYL METHACRYLATE: SYNTHESIS, CHARACTERIZATION and MECHANICAL PROPERTIES

M.Sc. THESIS

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Thesis Advisor: Assoc. Prof. Nermin ORAKDÖĞEN

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N,N-DİMETİLAMİNOETİL METAKRİLAT ESASLI MODİFİYE HİDROJELLER: SENTEZ, KARAKTERİZASYON VE MEKANİK ÖZELLİKLER

YÜKSEK LİSANS TEZİ

Tayyibe ÇELİK
(509121079)

Kimya Anabilim Dalı

Kimya Yüksek Lisans Programı

Tez Danışmanı: Doç. Dr. Nermin ORAKDÖĞEN

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Tayyibe ÇELİK, a **M.Sc.** student of ITU **Graduate School of Science Engineering and Technology** student ID **509121079**, successfully defended the **thesis** entitled "**MODIFIED HYDROGELS BASED on *N,N*-DIMETHYLAMINOETHYL METHACRYLATE: SYNTHESIS, CHARACTERIZATION and MECHANICAL PROPERTIES**", which she prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

Thesis Advisor :	**Assoc. Prof. Nermin ORAKDÖĞEN** Istanbul Technical University	.....
Jury Members :	**Prof. Dr. Oğuz OKAY** Istanbul Technical University	.....
	Asst. Prof. Gülşen AKIN EVİNGÜR Piri Reis University	.....

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To my beloved Sefa,

FOREWORD

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ABBREVIATIONS

DMAEMA : N,N-dimethylaminoethyl methacrylate
HEMA : 2-Hydroxyethyl methacrylate
PDMAEMA : Poly(N,N-dimethylaminoethyl methacrylate)
PHEMA : Poly(2-Hydroxyethyl methacrylate)
DEGDMA : Diethylene glycol dimethacrylate
APS : Ammonium persulfate
TEMED : N,N,N',N'-tetramethylethylenediamine
SCHs : Stimuli-responsive copolymer hydrogels
TEGDMA : Tetraethylene glycol dimethacrylate
LCST : Lower critical solution temperature
NIPA : N-isopropylacrylamide
PNIPA : poly(N-isopropylacrylamide)
Tg : Glass transition temperature

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LIST OF SYMBOLS

q_v	:	Equilibrium volume swelling ratio
q_w	:	Equilibrium weight swelling ratio
ν_2	:	Volume fraction of the network in the swollen gel
ν_2^0	:	Volume fraction of the network after the gel synthesis
V_{dry}	:	Volume of dry polymer
V_0	:	Volume of the gel after synthesis
$V_{swollen}$	:	Volume of the equilibrium swollen gel
m_{mon}	:	Amount of the monomer used in the synthesis
V_{tot}	:	Total volume of the pre-gel solution
$\rho_{pol.}$	:	Density of the polymer
n_{mon}	:	Mole number of the monomer used in the synthesis
C_0	:	Initial molar concentration of the monomer
$\overline{V_r}$	:	Molar volume of the polymer repeat units
m_0	:	Weight of the gel after the synthesis
$m_{swollen}$	:	Weight of the gel samples after equilibrium swelling
m_{dry}	:	Weight of the gel in the dry state
q_F	:	Dilution degree after the gel synthesis
D_{dry}	:	Diameter of the dry gel
D_0	:	Diameter of the gels after preparation
D	:	Diameter of the gels after equilibrium swelling
$\Delta G_{\text{swelling}}$	:	Change in the Gibbs free energy during the swelling process
ΔG_{mix}	:	Change in the free energy of mixing
ΔG_{el}	:	The free energy of elastic deformation
n_1	:	Number of moles of the solvent molecules
X	:	Crosslinker ratio
N	:	Number of segments between two successive crosslinks
$\overline{M_c}$	:	Molecular weight of network chain between two successive crosslinks
V_1	:	Molar volume of the solvent
V_m	:	Molar volume of the polymer solution
$\delta_{solvent}, \delta_{poly}$	:	Solubility parameter of the solvent and the polymer
χ_{12}	:	Interaction parameter between polymer and solvent
ν_e	:	Effective crosslink density
f	:	Deformation Stress
α	:	Deformation ratio
G_0, G	:	Elastic modulus of gels after preparation and equilibrium swelling
G_r	:	Reduced modulus
A	:	Cross-sectional area of the gel sample
l_0, l	:	Initial undeformed and deformed length
Δl	:	Change in the length of the gel after deformation

ϕ	:	Functionality of the crosslinks
M_t	:	Amount of water absorbed at time t
M_∞	:	Water uptake at equilibrium
n	:	A number to determine the type of diffusion
w_t	:	Weight of the wet copolymer hydrogel sample at time t
w_d	:	Weight of dry hydrogel
w_s	:	Weight of the swollen hydrogel at equilibrium

MODIFIED HYDROGELS BASED on *N,N*-DIMETHYLAMINOETHYL METHACRYLATE: SYNTHESIS, CHARACTERIZATION and MECHANICAL PROPERTIES

SUMMARY

The development of new polymeric biomaterials for medical and pharmaceutical purposes is of great interest to life-care science and biotechnology. Multipurpose smart hydrogel systems that swell and shrink in response to environmental stimuli such as temperature, pH, ionic strength and certain chemicals have attracted much attention in the past ten years. Depending on the type of monomers incorporated in the gel structure, they can be made to respond to a variety of external stimuli leading to what are known as stimuli-responsive hydrogels which are perhaps the most extensively studied classes of intelligent hydrogels. Among researchers there has been a long-standing interest in polymer systems that demonstrate a phase transition in response to variations in solution pH and temperature. Stimuli responsive hydrogels show the reversible volume changes with pH changes and on–off switching of electric field. Since the design of biomedical devices requires better understanding of the structure - property - response relationships of hydrogels, the precise information on the swelling behavior and the mechanical properties are required in their use in actuation and sensing applications. Understanding these properties have significant impact for the design of coatings for biosensors and for actuation devices based on stimuli-responsive hydrogels.

The aim of this study is to understand the swelling and elasticity behavior of acrylate-based copolymeric hydrogels under different conditions and to find quantitative correlation between the synthesis parameters and resulting physical properties. The critical questions that need to be addressed include: how the gel preparation conditions affect the macroscopic swelling properties of gels and how mechanical stability of resulting gels vary with these conditions. Thus, the experimental work of this consists two parts. In the experimental work of this thesis, the copolymeric hydrogels were prepared by free-radical crosslinking copolymerization of *N,N*-dimethylaminoethyl methacrylate (DMAEMA) with 2-Hydroxyethyl methacrylate (HEMA) in aqueous solution in the presence of diethylene glycol dimethacrylate (DEGDMA) as the crosslinker. It was proposed that through proper choice of monomers and other experimental conditions it is possible to tailor-make polymeric systems with specific properties. pH/temperature-induced phase transition behavior resulting from polymer-water and polymer-polymer interactions was demonstrated using poly(*N,N*-dimethylaminoethyl methacrylate-co-Hydroxyethyl methacrylate) P(DMAEMA-co-HEMA) copolymeric hydrogels.

The extent of swelling and mechanical properties of the copolymeric P(DMAEMA-co-HEMA) hydrogels was designed by changing the preparative conditions. The swelling behavior of copolymeric hydrogels was characterized by the equilibrium swelling measurements and the results were analyzed by using Flory-Rehner theory

of swelling equilibrium. Since the water adsorption characteristics of hydrogels have a significant influence on the diffusive behavior of small molecules into the gel, the swelling kinetics measurements were investigated to determine the swelling-deswelling rate of resulting gels. The diffusion of the swelling agent into the gel changes depending on the chemical composition and distribution of the hydrophobic-hdyrophilic monomer units along the macromolecular chain. The equilibrium swelling and dynamic swelling kinetics of hydrogels containing different amounts of HEMA were investigated under various experimental conditions such as temperature and pH of the swelling medium and in the presence of different types of salts. Compressive mechanical testing was performed at a state just after preparation and after equilibrium swelling in order to characterize the network structure of hydrogels such as the effective crosslinking density, the crosslinking efficiency and the number of segments between consecutive crosslinks. P(DMAEMA-co-HEMA) copolymeric hydrogels showed excellent compositional and mechanical features as well as unique tunable time-dependent swelling behavior. It was shown that these hydrogels possess tunable physicochemical properties that can be adjusted by changing copolymer composition.

This work shows that the extent of the swelling ratio, the swelling mechanism, the response time and the gel strenght of acrylate-based hydrogels could be modulated by controlling the factors such as the copolymer structure, the comonomer concentration, the temperature and the pH of the swelling media. The results also support that P(DMAEMA-co-HEMA) hydrogels with improved mechanical properties can be used as a water retainer for carrying substances in pharmaceutical and biomedical applications.

Keywords: *N,N*-dimethylaminoethyl methacrylate, hydrogel, elasticity, crosslinking, swelling, diffusion

N,N-DİMETİLAMİNOETİL METAKRİLAT ESASLI MODİFİYE HİDROJELLER: SENTEZ, KARAKTERİZASYON VE MEKANİK ÖZELLİKLER

ÖZET

Tıp ve eczacılık amaçlı yeni polimerik biyomalzemelerin geliştirilmesi, yaşam-bakım biliminin ve biyoteknolojinin büyük ilgi odağıdır. İlk olarak endüstriyel amaçlı kullanılmaya başlanan sentetik jeller ile ilgili çalışmalar sürekli gelişim göstermiş ve son yıllarda nanoteknoloji ve biyoteknoloji alanındaki gelişmelerle birlikte dikkate değer bir artış göstermiştir. Jellerle ilgili çalışmaların son zamanlarda popüler olmasının sebebi jellerin günlük yaşamımızda her yerde bulunmasıdır.

Genel bir tanımlamayla içerisine çözücü alarak şişme özelliği gösteren çapraz bağlı ağ yapısına sahip homo ya da kopolimerler polimerik jel olarak adlandırılmaktadır. Hidrojeller, polimerik jellerin önemli bir sınıfı olup hidrofillik ve suda çözünmemeleriyle karakterize edilen polimerik malzemelerdir. Bir polimerin çapraz bağlandığında hidrojel özelliği gösterebilmesi için ana zincir ya da yan dallarında hidroksil, karboksil, karbonil, amin ve amid gibi hidrojen bağı oluşturabilme yeteneğine sahip su sever grupları içermesi gerekmektedir**.** Hidrojellerin calışılan biyolojik ortama zarar vermemesi, yüksek verimle kullanılabilmesi ve hedeflenen amaca cevap verebilmesi için üç-boyutlu ağ yapılarının içinde bulundukları ortamla olan termodinamik etkileşimleri araştırmaya değer önemli bir konudur. Bu sistemler için gerekli olan şişme-büzülme, mekanik, morfoloji gibi pek çok özelliğin aynı hidrojel yapısı içinde bir araya gelmesi önemlidir.

Hidrojeller, doğal dokulara benzer kauçuğumsu yapıları, biyouyumluluk göstermeleri ve düşük yüzey gerilimlerinden dolayı insan dokusuna benzerliği nedeniyle biyomedikal ve farmasötik uygulamalarda ilgi çeken sentetik malzemelerdir. Reaksiyon koşulları değiştirilerek yapısal özelliklerinin istenildiği gibi ayarlanabilir olması ve ekonomik olarak elde edilebilmeleri nedeniyle, hidrojeller geniş kullanım alanlarına sahiptir. Biyomateryal özelliğe sahip hidrojeller, kontakt lenslerde, ilaç taşıyıcı ve kontrollü salınım sistemlerinde, sentetik kıkırdak, yapay kornea ve yapay organ yapımı, enzim tutuklama sistemleri, kemik hastalıkları tedavisinde ve omurlar arası boşlukların doldurulması için yardımcı materyal gibi pek çok uygulamada etkin olarak kullanılmaktadır.

Biyoteknolojik uygulamalarda kullanılan hidrojellerin, gerçek sistemlere benzer şekilde, dış ortamdan gelebilecek uyarılara cevap verebilecek özelliklere sahip olması istenmektedir. Sıcaklık, pH, iyonik kuvvet ve bazı kimyasallar gibi çevresel uyaranlara yanıt olarak şişen veya büzülen çok-amaçlı akıllı hidrojel sistemleri son on yılda oldukça dikkat çekmiştir. Jel yapısına katılan monomerlerin türüne bağlı olarak, çeşitli uyaranlara cevap verebilen ve akıllı polimerlerin üzerinde en çok çalışılan sınıfı olan "uyarı-cevap hidrojelleri" elde edilebilir.Uyarı-cevap hidrojelleri taşıdıkları fonksiyonel gruplar sayesinde veya kimyasal yapılarına bağlı olarak çevresel etkilere hacim değiştirerek yanıt verirler ve 'hacim faz geçişi' gösterirler.

Bu çevresel etkiler fiziksel ve kimyasal olmak üzere pH, sıcaklık, iyonik kuvvet, manyetik alan, elektrik alan ve metal gibi çok çeşitli olabilir.

Hacim faz geçişi, belli bir uyaran aralığında yavaş yavaş olabildiği gibi, ani/keskin bir değişim şeklinde de gözlenebilmektedir. Uyarı-cevap hidrojelleri, mikro yapılarında hidrofillikten hidrofobluğa ani ve tersinir geçiş yapabilme özelliklerinden dolayı yapay kas ve ilaç salım proseslerinde kullanılması öngörülmüştür. Biyomedikal cihazların tasarımı, hidrojellerin yapı-özellik-tepki ilişkilerinin daha iyi anlaşılması gerektirdiğinden, bu jellerin "hareket ve algılama" gerektiren uygulamalarda kullanılabilmeleri için şişme davranışları ve mekanik özellikleri ile ilgili kesin bilgilere ihtiyaç bulunmaktadır. Bu özelliklerin anlaşılması, biyosensörler için kaplama ve harekete duyarlı cihazların tasarımı için önemli bir etkiye sahiptir.

Bu çalışmanın amacı, farklı deneysel koşullar altında akrilat-bazlı kopolimerik hidrojellerin şişme ve elastisite davranışlarının anlaşılması, sentez parametreleri ve elde edilen fiziksel özellikler arasındaki ilişkilerin belirlenmesidir. Jel hazırlama koşullarının, jellerin makroskopik şişme özelliklerini nasıl etkilediği ve jellerin mekanik dayanıklılığının bu koşullar ile nasıl değiştiği araştırma kapsamında ele alınan kritik sorulardır.

Bu çalışmada kopolimerik hidrojeller, *N,N*-dimetilaminoetil metakrilat (DMAEMA) ile Hidroksietil metakrilat (HEMA) monomerinin sulu ortamda dietilenglikol dimetakrilat (DEGDMA) çapraz bağlayıcısının Ammonium persulfate - N,N,N',N'-tetramethylethylenediamine (APS-TEMED) redoks başlatıcı sistemi varlığında serbest radikal mekanizma ile kopolimerizasyonu sonucunda elde edilmiştir. Çıkış monomerlerinin ve diğer deney koşullarının uygun şekilde seçilmesiyle, belirli özelliklere sahip polimerik sistemlerin tasarımının mümkün olduğu ileri sürülmüştür. Poli(*N,N*-dimetilaminoetil metakrilat-ko-Hidroksietil metakrilat) P(DMAEMA-ko-HEMA) kopolimerik hidrojellerini polimer-su ve polimer-polimer etkileşimleri sonucu meydana gelen pH / sıcaklığa bağlı faz geçiş davranışları incelenmiştir.

Kopolimerik hidrojeller, deney koşulları ile şişme ve mekanik özellikleri kontol edilecek şekilde tasarlanmıştır. Kopolimerik jellerin şişme kapasiteleri ve şişme davranışı saf suda, farklı pH değerlerine sahip tampon çözeltilerde ve farklı iyonik şiddete sahip tuz çözeltileri içerisinde incelenmiş olup denge şişme ölçümleri ile karakterize edilmiştir ve sonuçlar Flory-Rehner denge şişme teorisi ile analiz edilmiştir.

Hidrojellerin su tutma özellikleri, küçük moleküllerin jel içine difüzyonunda önemli bir etkiye sahip olduğundan, hidrojellerin şişme kinetiği ölçümleri gerçekleştirilmiş ve şişme-büzülme kapasiteleri belirlenmiştir. Solvent moleküllerinin jel içine difüzyonu, kimyasal yapıya, polimer zincirlerinde ve ağyapıdaki hidrofobik-hidrofilik monomer birimlerinin dağılımına bağlı olarak değişim göstermektedir. Farklı miktarlarda HEMA içeren kopolimerik hidrojellerin şişme dengesine ve dinamik şişme-büzülme kinetiğine, şişme ortamının pH ve sıcaklığı gibi deneysel koşulların ve farklı tuzların etkisi incelenmiştir.

Hidrojellerin, etkili çapraz bağlanma yoğunluğu, çapraz bağlama verimliliği ve ardışık çapraz bağlar arasındaki segment sayısı gibi karakteristik ağyapı parametrelerinin belirlenmesi için, sentez sonrasında ve şişme dengesine ulaşıldıktan sonra tek eksenli sıkıştırma testleri uygulanmıştır ve Rubber elastisite teorisi kullanılarak jellerin mekanik davranışlarının belirlenmesi sağlanmıştır. P(DMAEMA-ko-HEMA) kopolimerik hidrojelleinin mükemmel yapısal ve mekanik özelliklerinin yanısıra zaman-bağlı şişme davranışlarının kontrol edilebilir olduğu

anlaşılmıştır. Hidrojellerin kopolimer bileşiminin değiştirilmesi ile ayarlanabilir fiziko-kimyasal özelliklere sahip olduğu gösterilmiştir.

Bu çalışma, akrilat bazlı hidrojellerin şişme oranı, şişme mekanizması, yanıt süresi ve jel mukavemeti derecesinin, kopolimer yapısı, komonomer konsantrasyonu, sıcaklık ve şişme ortamının pH'ı gibi deneysel etkenlerin denetlenerek modüle edilebileceğini göstermektedir. Sonuçlar, aynı zamanda iyileştirilmiş mekanik özellikler gösteren P(DMAEMA-ko-HEMA) hidrojellerinin ilaç ve biyomedikal uygulamalarda moleküllerin/ajanların taşınması için bir su tutucu olarak kullanılabilir olduğunu desteklemektedir.

Anahtar Kelimeler: *N,N*-dimetilaminoetil metakrilat, hidrojel, elastisite, çapraz bağlanma, şişme, difüzyon

1. INTRODUCTION

Hydrogels are three-dimensional structures generated from polymeric materials that are highly swollen with water, generally useful for bioapplications because of their ability to simulate biological tissues [1]. The elasticity and the equilibrium water content which are the most important hydrogel properties can be adjusted synthetically, thus affording investigators the ability to tailor the resulting materials depending on the type of the application [1,2].

As a typical class of soft and smart materials, stimuli-responsive copolymer hydrogels (SCHs) are able to significantly change their volume in response to small alterations of the external physicochemical factors such as pH, temperature, ionic strength, chemical matters, light sensitivity, electric and magnetic field [3-13]. Tertiary amino groups carrying (meth)acrylates, in particular *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA) has been attracting the attention of the researchers for many applications, the most of them being focused on the biological and therapeutic demands, biosensors, membranes, drug delivery systems, substrates for cell culture, isolation of biomolecules, enzyme activity control, smart switch, matter delivery and separator since they show compatibility with solution processing, such as micellization, thermo- and pH-sensitivity [14-25]. Poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA) hydrogel is a pH-responsive cationic polyelectrolyte with tertiary amino group, and it also has a temperature-responsiveness. The stimuli responsive behavior of PDMAEMA hydrogels is expected due to a conformation transition of PDMAEMA from the stretched to shrunken state after changes in pH and temperature. At pH values over the pKa of the cationic groups, the hydrogels are hydrophobic and excluded water from the system whereas at pH values lower than the pKa, the pendant tertiary amines are easily protonated, the hydrogels become hydrophilic and absorbed water. In these materials, pH and temperature sensitivity can be used to trigger the conformation transition to control their physico-mechanical and swelling properties since the

important factor governing their application is the response time of their volume changes [26-30].

Many scientists have concentrated on the synthesis of responsive copolymer hydrogels, amphiphilic stars, microcapsules and brushes including PDMAEMA [31-36]. Practical applications of PDMAEMA usually involve its chemical modification and physico-mechanical properties which has been achieved by its co-polymerization with hydrophilic/hydrophobic comonomers to improve the mechanical strength of hydrogel matrix. Ning et al. [34] synthesized PDMAEMA hydrogels by γ-irradiation and the property measurements of the hydrogels showed that the resulting hydrogels exhibited temperature sensitivity in a temperature range of 38–40^{o}C and pH sensitivity at pH 2.5. Horkay and coworkers [37] prepared pH-responsive hydrogels by crosslinking copolymerization of comonomers Hydroxypropyl methacrylate and DMAEMA with a crosslinker tetraethylene glycol dimethacrylate (TEGDMA) and studied the elastic shear modulus and swelling pressure of the hydrogels. At fixed pH, the elastic modulus decreases with increase in the swelling ratio in a power law dependence, as predicted by the Flory-Rehner model and thus the hydrogel stiffens as it swells in response to pH change. Satish and Shivakumar [38] investigated a selfregulating insulin delivery system consisting of P(DMAEMA-co-HEMA) hydrogels within in vivo conditions. The equilibrium swelling and insulin release was found to depend on the external glucose concentration and DMAEMA content of the hydrogels.

Since pH- and temperature responsive copolymeric PDMAEMA hydrogels are to be used in wide variety of applications, it is important to understand the detailed behavior of the PDMAEMA network under different conditions. Optimization of the swelling capacity for specific reasons is definitely an important goal. París and Quijada-Garrido [39] explored temperature- and pH-responsive behavior of poly(2-(2 methoxyethoxy)ethyl methacrylate-co-*N*,*N*-dimethylaminoethyl methacrylate) copolymeric hydrogels. The swelling properties of the hydrogels depend on temperature, however, it was also reported that the thermo-responsiveness depends on the pH. Lesho and Sheppard [40] examined the swelling -deswelling kinetics of pH-responsive crosslinked copolymers of HEMA with up to 20 mol% DMAEMA by measuring electrical conductivity. The agreement between the swelling data and buffer-mediated diffusion-reaction theory indicated that diffusive transport of

protons within the hydrogel is the rate-limiting step during a pH-induced change in hydration. To assess the role of swelling and cationic character on transfection which may affect DNA release, a series of pH-sensitive vehicles composed of DMAEMA and HEMA crosslinked with 3 mol% TEGDMA was prepared by You and Auguste [17]. Both the extent of swelling and the electrostatic interactions between the cationic DMAEMA and anionic DNA affect the rate of DNA release. Cheng and coworkers prepared amphiphilic gels based on DMAEMA modified with 1-bromoalkanes by radiation-induced polymerization and investigated adsorption of Cr(VI) ions. The length of alkyl side chain had significant influence on both adsorption rate and adsorption capacity of Cr(VI) ions into the resulting gels [23].

Moreover, Poly[(dimethylaminoethyl methacrylate)-co-(ethyleneglycol dimethacrylate)] copolymeric hydrogels prepared gamma radiation copolymerization were used as a carrier for anticancer delivery by Mazied et al. and their results showed that the ratio of EGDMA in the comonomer feeding solution has a great effect on the gel fraction and water content in the final hydrogel [24]. Zhang et al. [41] prepared poly[(dimethylaminoethyl methacrylate)-co-(diallyl dimethyl ammonium chloride)] P(DMAEMA-co-DADMAC) hydrogels by radiation induced copolymerization and investigated its application as a carrier for notoginsenoside delivery. Compared with PDMAEMA hydrogel, P(DMAEMA-co-DADMAC) showed enhanced equilibrium degree of swelling and the release of notoginsenoside can be controlled by adjusting the pH, ionic strength, temperature of solution as well as the composition and structure of the gel.

Since single-network hydrogels have weak mechanical properties and slow response at swelling, various efforts have been devoted to enhance the mechanical strength and swelling/deswelling response of PDMAEMA-based hydrogels. Physical properties including stiffness (elastic modulus) reflect intimately the chemical composition and the organization of the constituents at the molecular level. The high water content leads to low mechanical strength, however, which in some cases limits the field of applications. The mechanical performance of hydrogels can be improved by increasing the crosslink density, forming interpenetrated networks or inducing crystallization. One approach to modulate hydrogel strength is the introduction of the appropriate amount of a second monomer with hydrophobic character. The swelling kinetics of such systems is controlled mainly by the crosslink density. The diffusion

of the swelling agent into the gel will change depending on the chemical composition and distribution of the hydrophobic monomer units along the macromolecular chain. The water adsorption characteristics of hydrogels have a significant influence on the diffusive behavior of small molecules through the gel and the interfacial interactions.

While most of these earlier studies have focused on the effect of pH and temperature on the swelling capacity of PDMAEMA hydrogels, the effect of incorporation of hydrophilic/hydrophobic comonomer on the mechanical properties of PDMAEMA-based hydrogels has not been well-investigated, to date. From the viewpoint of applications, it would be favorable if the hydrogel could respond to two types of stimuli simultaneously, either mutually or independently, with particular emphasis on the pH and temperature stimuli. The copolymerization of 2-hydroxyethyl methacrylate (HEMA) with DMAEMA yields copolymeric hydrogels of varying physical and chemical properties, the degree of swelling, the mechanical strength, and the optical properties. In this thesis, it is aimed that the extent of the swelling and the mechanical properties of acrylate-based hydrogels could be designed to vary by changing the preparative conditions. This work has demonstrated that through proper choice of the monomers and other experimental conditions, it is possible to tailor-make stimuli-responsive systems with specific properties. In order to fabricate tough hydrogels with superior formability, a series of responsive hydrogels composed of *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA) and 2-hydroxyethyl methacrylate (HEMA) were prepared with different compositions by free radical crosslinking copolymerization. Hydrogels based on (Meth)acrylate polycations, such as PDMAEMA have shown promising activity, but their high cytotoxicity and lack of biodegradability limit their potential in biotechnology. Because of its hydrophilic characteristic, polymerization of 2-hydroxyethyl methacrylate (HEMA) produces hydrophilic materials, which generally possess excellent biocompatibility with living tissues and extremely low cytotoxicity. HEMA is a very good choice for making copolymeric hydrogels since they are widely used in cooling media, contact lenses, and material for drug delivery systems, in the manufacture of adhesives, paints, foods, and personal medicines. Therefore, the combination of both monomers will yield an interesting system with tuneable pH/temperature responsiveness, swelling capacity and improved mechanical properties which depend on the composition of the resulting copolymeric hydrogels.

2. HYDROGELS AS SMART MATERIALS

Hydrogels are three-dimensional polymer networks that are able to retain a large amount of water in their swollen state [42]. Hydrogels can be classified as natural or synthetic depending on the source of the constituting polymers. Hydrogels can be chemically crosslinked by covalent bonds, physically crosslinked by non-covalent interactions or crosslinked by a combination of both. Figure 2.1 represents the schematic view of crosslinked polymer network. The interactions responsible for the water sorption include capillary, osmotic and hydration forces, which are counterbalanced by the forces exerted by the crosslinked polymer chains in resisting expansion [43]. The equilibrium swollen state depends on the magnitudes of these opposing effects and determines the large extent of some important properties of the hydrogel, including internal transport, diffusion characteristics and mechanical strength.

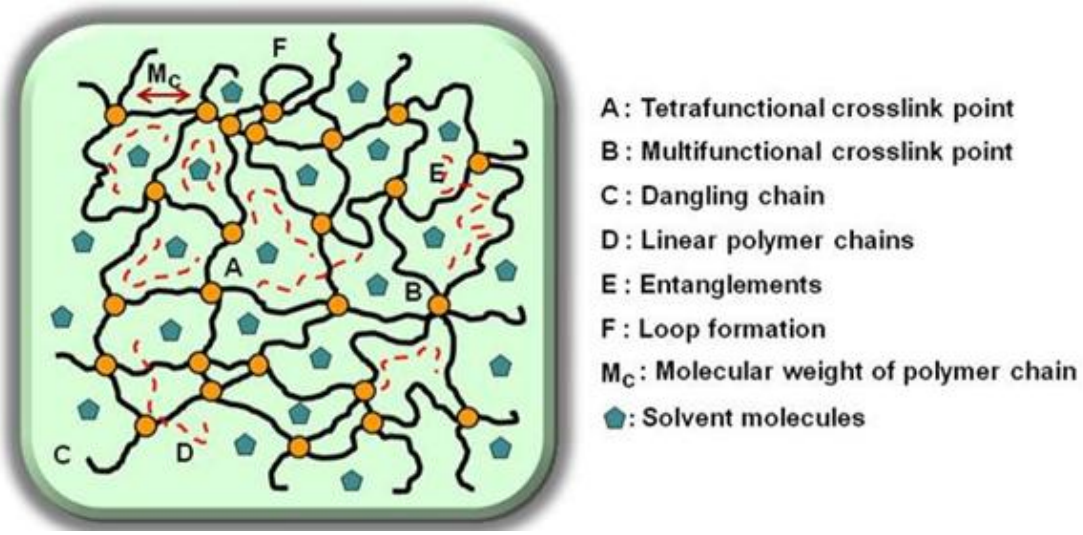

Figure 2.1 : Schematic view of crosslinked polymer network.

Many of these properties are governed not only by the degree of swelling, but also directly by the chemical nature of the polymer network and the network morphology. Due to their high water content, the properties of hydrogels resemble those of biological tissues, resulting in an excellent biocompatibility. Furthermore, their soft

and rubbery nature minimizes inflammatory reactions of the surrounding cells [44]. After their discovery in the 1960s by Wichterle and Lim [45] hydrogels were first successfully applied as contact lenses. Later, hydrogels have been frequently used as systems for the controlled delivery of biologically active agents. These hydrogels facilitate the localized and sustained release of a drug, thereby prevent the damage to the drug and allowing for relatively low doses.

The hydrogel products can be classified on different bases as detailed below:

i. Polymer gels can be classified as neutral or ionic gels depending on the type of the repeating units and the nature of the side groups on the polymer backbone. The neutral gels, for example, poly(vinyl alcohol), do not have the ionizable groups on the polymer backbone or the side chain. Thus, the swelling of these gels is independent of pH or ionic strength.

i. Polymer gels can be classified as neutral or ionic gels depending on the type of the repeating units and the nature of the side groups on the polymer backbone. The neutral gels, for example, poly(vinyl alcohol), do not have the ionizable groups on the polymer backbone or the side chain. Thus, the swelling of these gels is independent of pH or ionic strength. On the other hand, the ionic gels contain the ionizable functional groups. Therefore, they can be further classified as, anionic and cationic gels depending on the nature of the ionizable groups on their backbones. The anionic gels usually contain acid groups which form –COO- and swell at high pH and collapse at low pH values. In the unionized state, the hydrogen of the carboxylic group might be donated to a nearby electron-rich group to form hydrogen bonding which leads to the formation of polymer complexes. Poly(acrylic acid) and poly(methacrylic acid) are typical examples of the anionic gels. The cationic gels usually contain amino groups which form $–NH3^{+}$ and swell at low pH and collapse at high pH. Dimethylaminoethyl methacrylate (DMAEMA) and Diethylaminoethyl methacrylate (DEAEMA) are the typical cationic monomers.

ii. They can be homopolymer or copolymer networks based on the method of preparation.

iii. According to their mechanical and structural characteristics, they can be classified as affine or phantom networks.

iv. Polymer gels are random networks of flexible polymer chains and usually prepared by bulk, solution, emulsion or suspension polymerization of monomers in the presence of a crosslinking agent. According to the nature of the crosslinks between the monomers the gels are divided into two classes;

1- Chemical gels (where crosslinking is strong): These gels are created when the monomers form permanent covalent bonds. The gel network is permanent once formed and are stable against changes in thermodynamic parameters such as temperature.

2- Physical gels (where the bonds are weak): These gels are formed when the bonds between the units which make up the gel are due to some other physical mechanism. Since the bond are not chemical bonds, they can break or rebond by changes in thermodynamic parameters.

2.1 Stimuli Responsive Hydrogels

Stimuli-responsive hydrogels have gained the name of "smart materials" due to their unique ability to change volume or shape in response to environmental changes [46,47]. Hydrogels have been developed that display sensitivity towards a broad range of chemical or physical stimuli including pH [48], temperature [49], solvent composition [50], light [51], electric field [52], glucose [53] and more recently, biochemical agents such as proteases[54-58] and nucleotides[59]. Because the stimuli which caused the volume change response, can be used to perform mechanical work, thus stimuli-responsive hydrogels have potential applications in controlled drug delivery devices [60] biosensors [59] and scaffolds [61].

The stimuli-induced volume change usually arises from one of two major mechanisms: (1) changes in osmotic pressure or charge density (i.e., pH-responsive hydrogels); (2) changes in solvent affinity of the polymer backbone (i.e., temperature-responsive hydrogels). Of these systems, pH-responsive hydrogels have been the most extensively investigated systems . These materials usually contain acidic or basic pendent groups, such as carboxylic acids or tertiary amines. The pH-dependent ionization of the pendent groups generates fixed charges on the polymer backbone. Water diffuses into the hydrogel to lower the internal osmotic pressure caused by the fixed charges, which is the basis for hydrogel expansion. Figure 2.2 shows the response of the crosslinked polymer network towards pH changes.

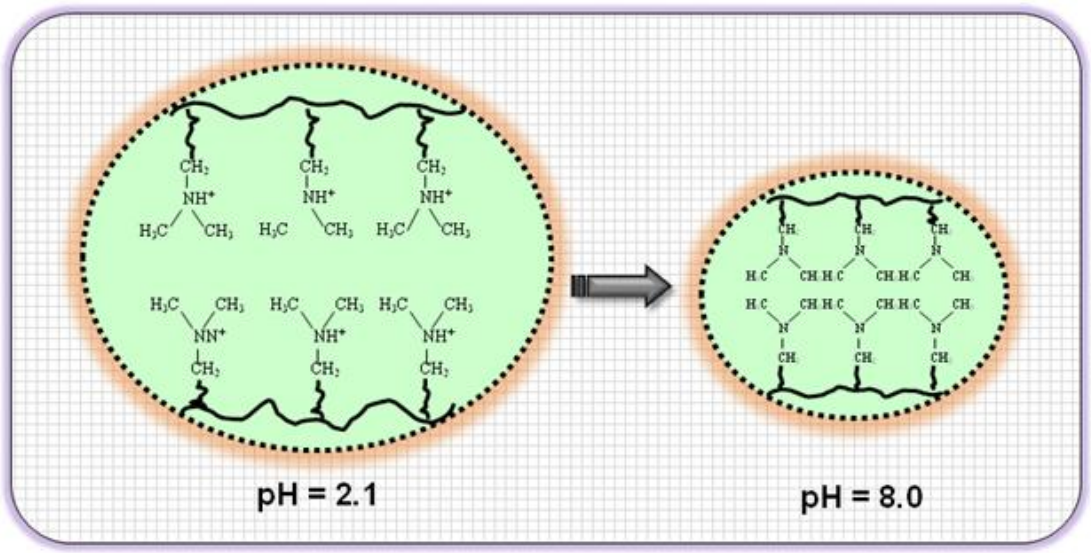

Figure 2.2 : Illustration of swelling response of a PDMAEMA gel according to change in pH of the swelling medium.

For temperature-responsive hydrogels, the polymers contain both hydrophobic and hydrophilic segments. At low temperatures the hydrophilic portions of the polymer dominate and allow the adsorption of water. Once the temperature of the solution increases above the lower critical solution temperature (LCST) of the polymer, however, the hydrophobic interactions become stronger causing a strengthened interaction between polymer chains. The collapse of the polymer chains leads to a shrinking of the hydrogel structure and the expulsion of water. The volume transitions can also arise from changes in hydrogel crosslink density. Because the hydrogel's structural rigidity is based on the crosslinking of polymer chains, the cleavage of the crosslinks can lead to a swelling or complete dissolution of the hydrogel. The crosslink density approach has provided the greatest opportunity for biomacromolecule sensing.

Many physical and chemical stimuli have been applied to induce various responses of the smart hydrogel systems. Figure 2.3 shows the volume changes of a stimuli-responsive hydrogel and stimuli types. The physical stimuli include temperature, electric fields, solvent composition, light, pressure, sound and magnetic fields, whereas the chemical or biochemical stimuli include pH, ions and specific molecular recognition events.

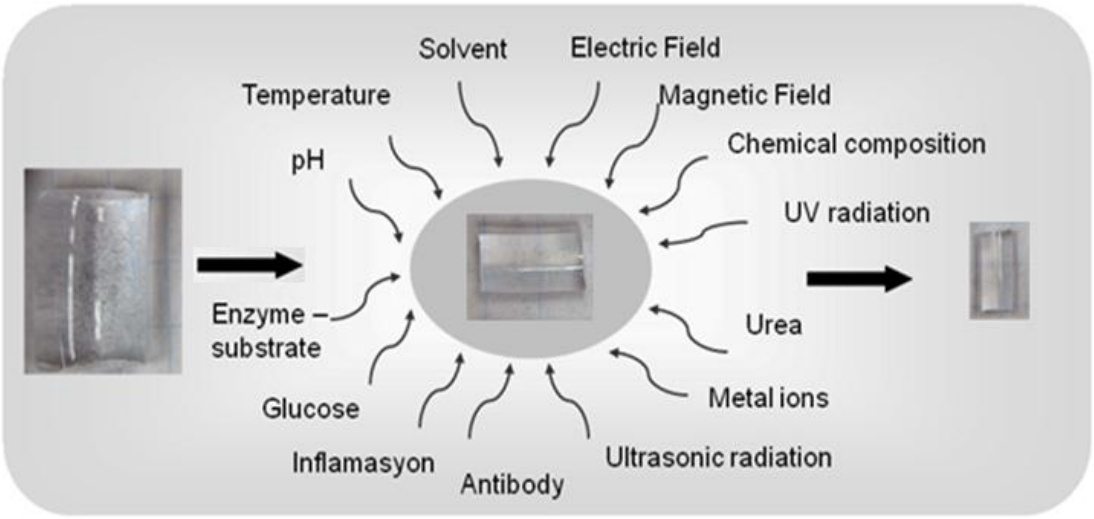

Figure 2.3 : Schematic view of stimuli-responsive hydrogels and stimulus types.

2.1.1 pH-sensitive hydrogels

pH-sensitive polymers are polyelectrolytes that bear in their structure weak acidic or basic groups that either accept or release protons in response to changes in environmental pH. The pendant acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacids or monobases. However, complete ionization on polyelectrolytes is more difficult due to electrostatic effects exerted by other adjacent ionized groups. This makes the apparent dissociation constant (Ka) different from that of the corresponding monoacid or monobase.

By generating the charge along the polymer backbone, the electrostatic repulsion results in an increase in the hydrodynamic volume of the polymer. This transition between tightly coiled and expanded state is influenced by any condition that modify electrostatic repulsion, such as pH, ionic strength, and type of counterions. The transition from collapsed state to expanded state has been explained by changes in the osmotic pressure exerted by mobile counterions neutralizing the network charges [62].

The pH range in which a reversible phase transition occurs can be generally modulated by two strategies:

1. Selecting the ionizable moiety with a pKa matching the desired pH range. Therefore, the proper selection between polyacid or polybase should be considered for the desired application.

2. Incorporating hydrophobic moieties into the polymer backbone and controlling their nature, amount and distribution. When ionizable groups become neutral – non-ionized- and electrostatic repulsion forces disappear within the polymer network, hydrophobic interactions dominate. The introduction of a more hydrophobic moiety can offer a more compact conformation in the uncharged state and a more accused phase transition. The hydrophobicity of these polymers can be controlled by the copolymerization of hydrophilic ionisable monomers with more hydrophobic monomers with or without pH-sensitive moieties, such as 2-hydroxyethyl methacrylate, methyl methacrylate and maleic anhydride.

Hydrogels that have the ability to respond to pH changes have been studied extensively over the years. These gels typically contain ionizable side groups such as carboxylic acids or amine groups [63]. Poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly (diethylaminoethyl methacrylate) (PDEAEMA), and poly(dimethylaminoethyl methacrylate) (PDMAEMA) are the most commonly investigated ionic polymers. Siegel and Firestone studied the swelling behavior of hydrophobic hydrogels of PDMAEMA and poly(methyl methacrylate) [64]. These systems were collapsed in solutions of pH greater than 6.6. However, in solutions of pH less than 6.6, such systems swelled due to protonation of the tertiary amine groups. Peppas and co-workers have studied the swelling behavior of cationic copolymers of P(DEAEMA-co-HEMA) and P(DMAEMA-co-HEMA) [65]. It was found that below pH 7, these gels swell and in basic solutions they collapse. And also it was seen that these gels swelled to a greater degree than those prepared by Siegel [66].

2.1.2 Temperature-sensitive hydrogels

Temperature-sensitive hydrogels are one of the most commonly studied class of environmentally sensitive polymer systems in drug delivery research [67]. Many polymers exhibit a temperature responsive phase transition property. Bearing hydrophobic groups, such as methyl, ethyl and propyl groups in their network structure is the common characteristic of temperature-sensitive polymers.

Most polymers increase their water-solubility as the temperature increases. Polymers with LCST, however, decrease their water-solubility as the temperature increases. Hydrogels made of LCST polymers shrink as the temperature increases above the

LCST[13]. The temperature-dependent hydrogels are made of polymer chains that either possess moderately hydrophobic groups or contain a mixture of hydrophilic and hydrophobic segments. At lower temperatures, hydrogen bonding between hydrophilic segments of the polymer chain and water molecules are dominates, leading to enhanced dissolution in water. As the temperature increases, however, hydrophobic interactions among hydrophobic segments become strengthened, while hydrogen bonding becomes weaker. The net result is shrinking of the hydrogels due to inter-polymer chain association through hydrophobic interactions.

In general, as the polymer chain contains more hydrophobic constituent, LCST becomes lower [68]. The LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic segment of the polymer. One way is to make copolymers of hydrophobic and hydrophilic monomers. N-isopropylacrylamide (NIPA) is the one of the most widely studied temperature-sensitive polymer. The copolymerization of NIPA with different types of monomers results in hydrogels with more versatile properties, such as faster rates of shrinking when heated through the LCST [69], and sensitivity to additional stimuli.

As a cationic polyelectrolyte, PDMAEMA shows both temperature- and pH-responsive swelling behavior. Since N,N-dimethylaminoethyl methacrylate (DMAEMA) has a structure similar to N-isopropylacrylamide (NIPA), PDMAEMA shows a temperature sensitivity similar to poly(N-isopropylacrylamide) (PNIPA) [70,71]. Thus, PDMAEMA hydrogels also show controllable volume changes in response to small variation of temperature in the solution condition. The phase transition temperature of PDMAEMA hydrogels in aqueous solutions falls in the wide range of 38–50 °C [72,73].

3. SWELLING BEHAVIOR OF HYDROGELS

3.1 Swelling Process and Swelling Capacity

The favourable characteristic property of hydrogels is their ability to swell, when immersed into a thermodynamically compatible solvent. If a dried hydrogel is placed in a solvent, the hydrogel absorbs the solvent and its volume increases sometimes up to several thousand times. This phenomenon is called the swelling process. The swelling of hydrogels is a complex phenomenon resulting from the interplay of molecular architecture of the network and the specific polymer-solvent interactions.

The driving force behind the gel swelling is the free energy of mixing of the polymer and solvent. If the polymer molecules making up the gel are not joined together, they would dissolve in the solvent to decrease the free energy of mixing, and eventually would be distributed. However, the polymers in a gel are connected, and so if the gel absorbs enough solvent it can attain an equilibrium state since there are two competing factors that determine its volume. One factor is the free energy of mixing of the gel and the solvent, which tries to increase the gel volume. The other factor is the change in elastic energy of the gel when the volume is varied, which acts to hinder the volume expansion.

The degree of swelling is one of the essential parameters to characterize the gels. Since the gel can be regarded as a container of solvent made of a three dimensional mesh, one can investigate the molecular interaction between the polymer network and the solvent by simply measuring the degree of swelling[74]. In a dried state, the gel is a solid material. However, the gel can take several hours to days to swell until it reaches the swelling equilibrium when the solvent is added.

Figure 3.1 represents the swelling and drying process of polymer gel with characteristic parameters, such as; the diameter, weight and volume which are denoted by D, m and V, respectively. The two types of swelling ratio of the hydrogels can be described as:

1) The equilibrium volume swelling ratio (qv):

$$q_v = \frac{\text{volume of swollen gel}}{\text{volume of dry gel}} = \frac{V_{swollen}}{V_{dry}} \qquad \textbf{(3.1)}$$

2) The equilibrium weight swelling ratio (qw) :

$$q_w = \frac{\text{weight of swollen gel}}{\text{weight of dry gel}} = \frac{m_{swollen}}{m_{dry}} \qquad \textbf{(3.2)}$$

where $V_{swollen}$, V_{dry} and $m_{swollen}$, m_{dry} are the volumes and the weights of the gels in the swollen state and the dry state, respectively. For the determination of both swelling ratios q_v and q_w, the volumetric and gravimetric techniques can be used as will be described in Section 5.2.1.

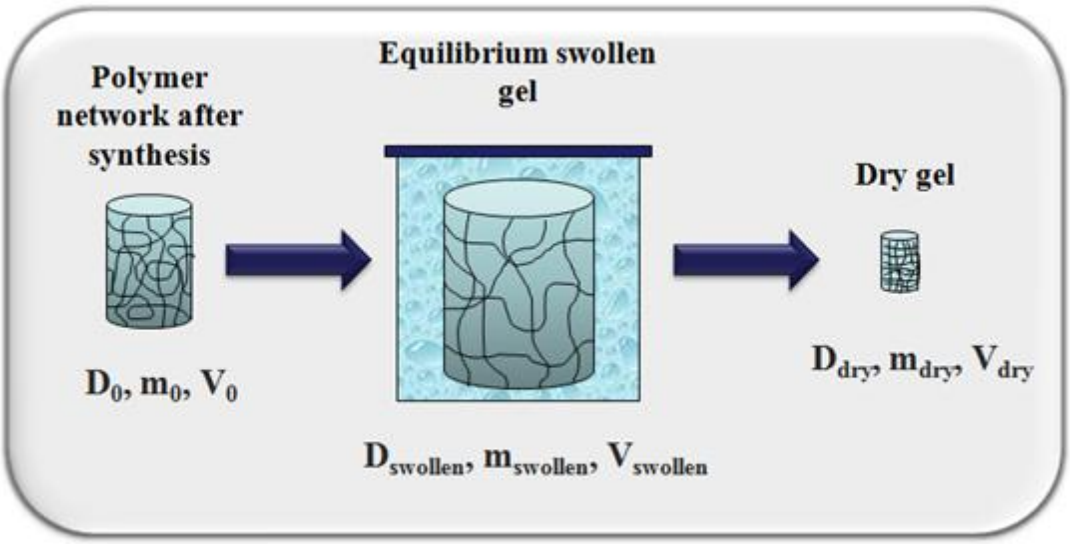

Figure 3.1 : A schematic representation of swelling process of polymer network in a solvent until the equilibrium swelling and further drying process of polymer gel.

Figure 3.2 shows schematically the differences of two characteristic synthesis parameters, namely, ν_2 and ν_2^0. ν_2 is the volume fraction of the network in the swollen gel and can be defined as the ratio of volume of dry polymer in the swollen gel to the total volume of the swollen gel by:

$$\nu_2 = \frac{\text{volume of dry gel}}{\text{volume of the equilibriu m swollen gel}} = \frac{V_{dry}}{V_{swollen}} \qquad \textbf{(3.3)}$$

On the other hand, ν_2^0 is the volume fraction of the network after the gel synthesis and corresponds to the ratio of the volume of dry polymer to the volume of the gel after synthesis as follows:

$$\nu_2^0 = \frac{\text{volume of dry gel}}{\text{volume of the gel after synthesis}} = \frac{V_{dry}}{V_0} \qquad \textbf{(3.4)}$$

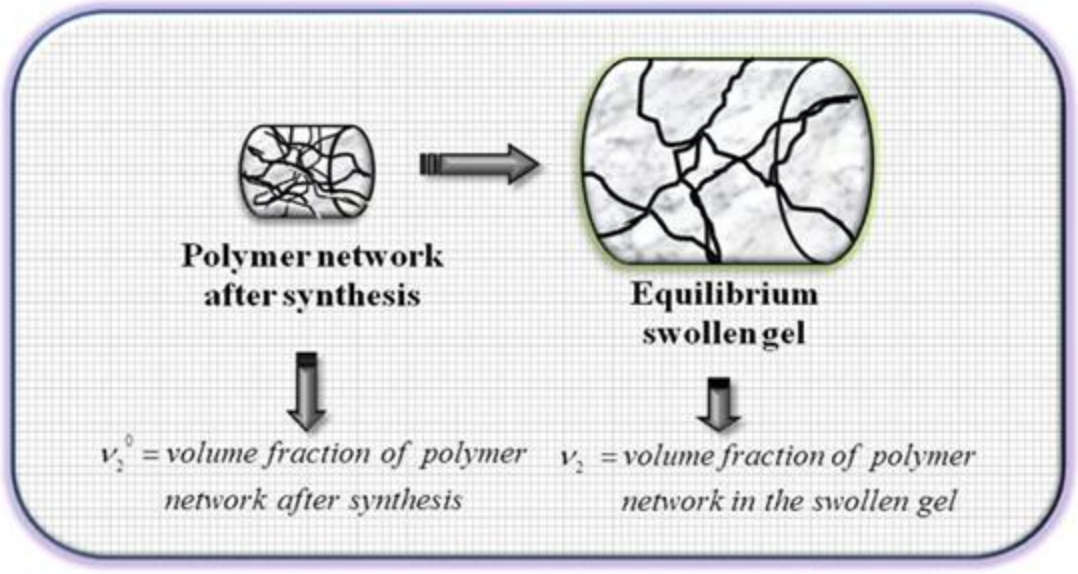

Figure 3.2 : The volume fractions of the network after equilibrium swelling and after gel synthesis which is denoted by ν_2 and ν_2^0 , respectively.

Equation (3.1) can be rewritten by using the definition of ν_2 in Equation (3.3) as follows:

$$q_v = \frac{V_{swollen}}{V_{dry}} = \frac{1}{\nu_2} \qquad \textbf{(3.5)}$$

One of the difficulties of the determination of the swelling ratio, q_v is the measurement of the volume of dry gel due to the deformation of the shape of the gel. The gels are usually dried in vacuum and transferred from a rubbery to the glassy state.

During this process, the cylindrical shape of the gel sometimes undergoes deformation and the volume determination of dry gel becomes difficult. However, the volume of the swollen gel can be determined easily by measuring the diameter of the swollen gel sample by a calibrated digital compass. In this case, it is more

convenient to write the equilibrium volume swelling ratio of the gels in terms of the volume of the gel after synthesis, i.e.,

$$q_v = \left(\frac{\text{volume of the equilibriu m swollen gel}}{\text{volume of the gel after synthesis}} \right) \left(\frac{\text{volume of the gel after synthesis}}{\text{volume of dry gel}} \right) \quad \textbf{(3.6)}$$

Thus, Equation (3.6) can be rewritten in terms of the volume fractions ν_2 and ν_2^0, by combining Equation (3.4) and (3.5) as follows:

$$q_v = \frac{1}{\nu_2} = \frac{V_{swollen}/V_0}{\nu_2^0} \quad \textbf{(3.7)}$$

Moreover, the equilibrium swelling ratio of gels $V_{swollen}/V_0$, can be calculated as:

$$V_{eq} = \frac{V_{swollen}}{V_0} = \left(\frac{D}{D_o} \right)^3 \quad \textbf{(3.8)}$$

where D and D_0 are the diameter of the gels after equilibrium swelling and after preparation, respectively. Hence, by combining Equation (3.7) and (3.8), the equilibrium volume swelling ratio of the gels can be written in terms of the synthesis parameters, ν_2 and ν_2^0, and the diameter of the gels:

$$q_v = \frac{1}{\nu_2} = \frac{V_{swollen}/V_0}{\nu_2^0} = \frac{(D/D_0)^3}{\nu_2^0} \quad \textbf{(3.9)}$$

Assuming additivity of volumes within the swollen gel, the interrelation between q_v and q_w is given by:

$$q_v = 1 + \frac{(q_w - 1)\rho}{d_1} \quad \textbf{(3.10)}$$

where d_1 is the density of the swelling agent and ρ is the density of the polymer. If it is assumed that the monomer conversion is complete after the crosslinking copolymerization, then the volume fraction of the polymer network after synthesis ν_2^0 can be written in terms of the initial molar concentration of the monomer, C_0 (mol/L):

$$\nu_2^{\,0} = C_0 \overline{V}_r \qquad \textbf{(3.11)}$$

where $\overline{V}_r$ is the molar volume of the polymer repeat units (in ml/mol). By using Equation (3.11), the theoretical value of $\nu_2^{\,0}$ can be calculated from the initial monomer concentration used in the gel preparation. The volume fraction of the polymer network after synthesis $\nu_2^{\,0}$ can be calculated experimentally by using the equation:

$$\nu_2^{\,0} = \left[1 + \frac{q_F - 1}{d}\rho\right]^{-1} \qquad \textbf{(3.12)}$$

where q_F is the dilution degree after the gel synthesis which can be defined as:

$$q_F = \frac{\text{weight of gel after synthesis}}{\text{weight of dry gel}} = \frac{m_0}{m_{dry}} \qquad \textbf{(3.13)}$$

3.2 Equilibrium Swelling Theory of Hydrogels

During the past decades the theoretical and experimental efforts have been done in order to better understand the swelling phenomenon in the polymer gels. A large portion of this work was developed by Paul J. Flory whose concepts and basic approach are still largely used to improve the swelling of gels [75].

During the swelling process, the network chains are forced to attain more elongated, less probable configurations. The absorption of the solvent by the gel causes the network to expand and its chains to stretch. As a result, the chains making up the network is assumed in a stretched conformation as the network swells. Hence, like pulling a spring from both ends, a decrease in chain configurational entropy is produced by swelling. Opposing this, an increase in entropy of mixing of solvent with polymer accompanies the swelling. In addition, the enthalpy of mixing also controls the extent of swelling.

Accordingly, mainly three forces arise from different sources during the process of swelling:

1. The entropy change caused by mixing polymer and solvent: The entropy change from this source is positive and favors swelling.

2. The entropy change caused by reduction in the number of possible chain conformations as the polymer network swells: The entropy change from this source is negative and opposes swelling.

3. The heat of mixing of polymer and solvent, which may be positive, negative, or zero. Usually, it is slightly positive and opposing mixing.

The combination of thermodynamic and elasticity theories states that the crosslinked polymer gel which is immersed in the solvent and allowed to reach equilibrium with its surroundings is subject only to two opposing forces; one is the swelling force which is the interaction between the polymer and the solvent. The other is the elastic force which depends on the degree of crosslinking. A state of equilibrium swelling is reached when these two forces are equal.

The Flory-Rehner theory has been most widely used to explain the swelling process of gels that do not contain ionic moieties[76]. A basic element of the Flory-Rehner theory is the so-called "additivity assumptions", which states that the change in the Gibbs free energy ($\Delta G_{\text{swelling}}$) during the swelling process could be expressed as the sum of the individual free energy terms, i.e., the changes in the free energy of mixing ΔG_{mix}, in the free energy of elastic deformation ΔG_{el} [75-77]:

$$\Delta G_{swelling} = \Delta G_{mix} + \Delta G_{el} \qquad \textbf{(3.14)}$$

where ΔG_{mix} is the free energy change of mixing of the solvent molecules and the polymer chains. This term is a measure of the compatibility of the polymer with the solvent molecules and given by:

$$\Delta G_{mix} = RT\left[n_1 \ln \nu_1 + n_2 \ln \nu_2 + \chi n_1 \nu_2\right] \qquad \textbf{(3.15)}$$

where n is the mole number, ν is the volume fraction, χ is the interaction parameter between the solvent (1) and polymer network (2), respectively. ΔG_{el} is the elastic free energy change due to the configurational rearranging and stretching of the crosslinked network chains during the swelling process and can be given as:

$$\Delta G_{el} = \frac{3}{2}\bar{\nu}RT\left[\left(\frac{\nu_2^{\,0}}{\nu_2}\right)^{2/3} - 1 - \ln\left(\frac{\nu_2^{\,0}}{\nu_2}\right)^{1/3}\right] \quad \textbf{(3.16)}$$

where $\bar{\nu}$ is the number of moles of polymer chains in a unit volume of dry polymer network. Substitution of the Equations given for ΔG_{el} and ΔG_{mix} into the Equation (3.14) gives the free energy equation of swelling for nonionic polymer networks as follows:

$$\Delta G_{swelling} = RT\left[n_1 \ln \nu_1 + n_2 \ln \nu_2 + \chi\, n_1\nu_2 + \frac{3}{2}\bar{\nu}\left\{\left(\frac{\nu_2^{\,0}}{\nu_2}\right)^{2/3} - 1 - \ln\left(\frac{\nu_2^{\,0}}{\nu_2}\right)^{1/3}\right\}\right] \quad \textbf{(3.17)}$$

Since the chemical potential of a given component is defined as the partial derivative of the free energy with respect to the number of moles of that component, the excess chemical potential of solvent can be calculated by differentiation of the total free energy of swelling $\Delta G_{swelling}$ with respect to the number of moles n_1 of the solvent molecules as:

$$\left(\frac{\partial \Delta G_{swelling}}{\partial n_1}\right)_{T,P} = \Delta\mu_1 \quad \textbf{(3.18)}$$

A gel is subjected to a swelling pressure π which is expressed as the sum of three components corresponding to each contribution to ΔG. The equilibrium condition is obtained when the swelling pressure is set equal to zero. This may be written as follows:

$$\pi = \frac{-\left(\mu_1^{\,gel} - \mu_1^{\,sol}\right)}{V_1} = \frac{-\Delta\mu_1}{V_1} = 0 \quad \textbf{(3.19)}$$

where V_1 is the molar volume of the solvent. $\Delta\mu_1$ is the chemical potential of the solvent which can be given as follows:

$$\Delta\mu_1 = RT\left[\ln(1-\nu_2)+\nu_2+\chi\,\nu_2^{\,2}+\frac{1}{N}\left(\nu_2^{1/3}\left(\nu_2^{0}\right)^{2/3}-\nu_2/2\right)\right] \qquad \textbf{(3.20)}$$

At equilibrium, the difference between the chemical potentials of the solvent outside and inside the gel must be zero so:

$$\ln(1-\nu_2)+\nu_2+\chi\nu_2^{\,2}+\frac{1}{N}\left(\nu_2^{1/3}\left(\nu_2^{0}\right)^{2/3}-\frac{\nu_2}{2}\right)=0 \qquad \textbf{(3.21)}$$

This equation is called Flory-Rehner Equation for non-ionic gels and gives a quantitative relation between the swelling degree and the network properties such as N, $\overline{M}_c$ and $\nu_2^{\,0}$.

3.3 Parameters Affecting Swelling Behavior of Hydrogels

The swelling properties of hydrogels is strongly affected by the interaction between the solvent and the network. The gel swells to a large extent in a good solvent, whereas it shrinks to a compact form in a poor solvent. The swelling is accompanied by diffusion of the polymer network in the solvent rather than the solvent diffusion into the polymer network, therefore both the gel elasticity and the friction between the polymer network and the solvent determine the gel swelling[78].

i. The initial molar concentration of the monomer, C_0 (mol/L): The swelling behavior of the gels sensitively depend on the degree of dilution at which they are formed. The degree of dilution of the polymer networks after their preparation is denoted by $\nu_2^{\,0}$, the volume fraction of the network after synthesis. Equation (3.11) shows that $\nu_2^{\,0}$ is proportional to the initial molar concentration of the monomer, C_0. This means that, the higher the initial concentration of the monomer, C_0, the higher the value of $\nu_2^{\,0}$.

On the other hand, according to Equation (3.7), $\nu_2^{\,0}$ is inversely proportional to the equilibrium volume swelling ratio q_v. Hence, the equilibrium swelling ratio of the gels with constant crosslink density decreases with increasing monomer concentration. The higher the initial monomer concentration, the larger the effective crosslink density of the hydrogels and the smaller their swelling capacity.

ii. The crosslinker concentration, i.e. the crosslinker ratio, *X*: The equilibrium volume swelling ratio of the gels decreases with increasing crosslinker ratio. The crosslinker ratio can be defined as the number of crosslinks per unit volume of the polymer network and written as the mole ratio of crosslinker to the monomer:

$$X = \frac{[\text{crosslinker}]}{[\text{total monomer}]} = \frac{1}{2N} \qquad \textbf{(3.22)}$$

where *N* is the number of segments between two successive crosslinks. Increasing monomer concentration also increases the effective crosslink density ν_e of the gels due to the more efficient consumption of the crosslinker in concentrated monomer solutions. Increasing crosslink density will decrease the swelling of gels due to decreasing number of segments *N* and the molecular weight of network chain $\overline{M}_c$ between two successive crosslinks which are also shown schematically in Figure 3.3.

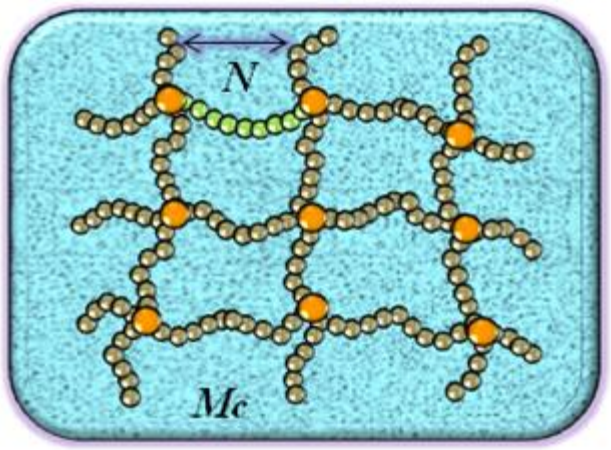

Figure 3.3 : A schematic representation of crosslinked polymer network. The number of segments *N* and the molecular weight of the network chain $\overline{M}_c$ between two successive crosslinks are also indicated in the figure.

It was also found that the dependence of the swelling rate on the crosslinker content shows two different regimes. Below a critical crosslinker concentration, increasing the crosslinker concentration decreases the rate of swelling of the networks. Because, rising the crosslinker content in the gel brings about a decrease in the mesh size of the gel network and the diffusion of the solvent molecules into the gel networks becomes difficult. Thus the gel with a high amount of crosslinker absorbs less amount of solvent in the equilibrium swelling state.

The higher the crosslinker content, the lower the swelling capacity of the gels. However, above the critical crosslinker concentration, although the swelling capacity of the network continue to decrease, the rate of swelling rapidly increases with increasing crosslinker content, which is opposite to what observed below the critical value. This point can be explained with the formation of heterogeneous structures in the polymer network. Below the critical crosslinker concentration, the network consist of aggregates of spherical domains which are called as microspheres.

After passing the critical crosslinker concentration, the network structure changes from homogeneous to heterogeneous ones. Further increase of the crosslinker content increases both the rate of swelling and the porosity of the network.

iii. The solvent quality and the interactions between polymer and solvent: The degree of swelling of the gels also depends on the compatibility of the solvent with the polymer network. The quality of the solvent may be expressed by the parameter χ or χ_{12} (in which the subscripts 1 and 2 denote the solvent and polymer, respectively). The interaction parameter is used to indicate whether a solvent is good or poor for the polymer. A good solvent has a low value of χ_{12} while a poor solvent has a high value of χ_{12}. In good solvents, the polymer network chains are in the extended conformation due to the strong molecular interaction between the polymer segment and the solvent. Thus, the degree of swelling at equilibrium in a good solvent increases with decreasing crosslinking.

On the other hand, in poor solvents, the molecular interaction between the polymer segment and the solvent molecules is not favored and the polymer-polymer contacts are preferred. The polymer segments reduce their resistance against each other and an attractive force developed between them. Thus, the polymer chains tend to shrink. The relation between the interaction parameter and the solubility parameter of the solvent and the polymer can be given through the equation as:

$$\chi = V_m \frac{(\delta_{solvent} - \delta_{polymer})^2}{RT} \qquad \textbf{(3.23)}$$

where V_m is the molar volume of the polymer solution and δ denotes the solubility parameter of the solvent and the polymer.

iv. The ionic group concentration: The swelling behavior is also dependent on the presence of the ionic groups in the network chains. If the network chains of the gel carry ionic groups also called charged units, the gel swells much more than the corresponding uncharged gel. The reason of this excess swelling is the existence of mobile counterions in the gel and the additional swelling forces due to the electrostatic repulsion between like charges on the polymer chains. As the ionic group concentration increases, the counterions concentration inside the gel also increases to maintain the electroneutrality condition. As a result, the difference between the counterion concentration inside and outside the gel increases with increasing the ionic group concentration, which creates an additional osmotic pressure that expands the gel.

v. External factors: Some of the external parameters affecting the swelling of hydrogels include pH, ionic strength, temperature, solvent composition and electromagnetic radiation [79-81].

3.4 Phase Transition of Polymer Gels

Analogous to a single chain that exhibits a coil-globule transition, the hydrogels sometimes undergo reversible discontinuous or continuous volume change when it is stimulated by chemical or physical factors. The volume phase transition means a dramatic volume change of the gel between its swollen and collapsed states induced by a tiny environmental change. In a sense, the volume phase transition of gels is a macroscopic manifestation of a coil-globule transition of polymer chains. The microscopic view of volume phase transition are shown in Figure 3.4.

The phase transition in polymer gels has been studied for about two decades since its theoretical prediction by Dusek and Patterson as early as 1968 [82]. They suggested that when the external forces are applied to the gels, the gel volume might undergo discontinuous change. The experimental verification was first made by Tanaka in 1978 using hydrolysed poly(acrylamide) gels swollen in water/acetone[49]. The gels 19 of various degree of hydrolysis were placed in acetone-water mixtures with different concentrations of acetone at room temperature. After one day, it was found that half of the gels is in a swollen state and half of the gels is in a collapsed state. Thus, the volume phase transition of the gels was discovered and opened a new aera of the study of the polymer gels.

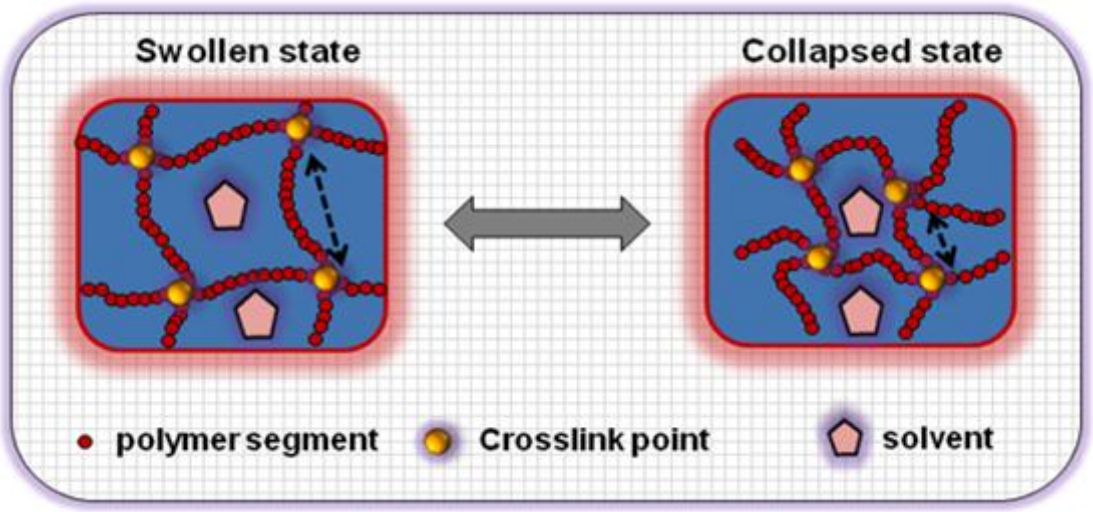

Figure 3.4 : The microscopic view of phase transition of polymeric gel-folding and unfolding of polymer network.

The volume phase transition of polymer gel is a result of a competitive balance between repulsive forces that act to expand the polymer network and attractive forces that act to shrink the polymer network. The attractive forces include van der Waals[48], hydrophobic interaction[83,84], and hydrogen bonding[85,86]. The repulsive forces include the electrostatic interaction between the polymer charges of the same kind and the osmotic pressure by the counter ions[87].

The major attraction force between the polymer chains is the van der Waals force. The volume phase transition of the partially hydrolyzed poly(acrylamide) gel is believed to be due to the van der Waals interaction. A poor nonpolar solvent must be added to a good solvent in order to increase this interaction large enough to induce the volume phase transition of the gel[81].

3.5 Diffusion Kinetics of Hydrogels

Swelling can be defined as a transition from unsolvated glassy or partially rubbery state to a relaxed rubbery region. When the polymer is in the rubbery state, polymer chains will have a high mobility that allows easier penetration of the solvent into the hydrogel. This situation can be divided into two categories: first, is the Fickian or Case I transport, which appears when the glass transition temperature (Tg) of polymer is well below the experiment temperature. Here, the solvent diffusion rate, R_{diff}, is clearly slower than the polymer chain relaxation rate, R_{relax}, ($R_{diff} << R_{relax}$). Secondly, Non-Fickian diffusion, which appears when the Tg of polymer is well

above the experimental temperature. In this situation, the polymer chains are not sufficiently mobile to permit urgent penetration of water into the polymer core [88].

Non-Fickian diffusion processes can also be classified as Case II transport and anomalous transport, respectively . When the diffusion rate is higher than the relaxation rate ($R_{diff} >> R_{relax}$), Case II transport exists. The anomalous transport is observed when the diffusion and relaxation rates are comparable ($R_{diff} \approx R_{relax}$).

A simple and useful empirical equation, so-called power law equation, is commonly used to determine the mechanism of diffusion in polymeric networks [89]:

$$F = \frac{M_t}{M_\infty} = \frac{WU_{(t)}}{SR_{(eq)}} = kt^n \qquad \textbf{(3.24)}$$

where F denotes the water fraction at time t, M_t is the amount of water absorbed at time t, M_∞ is the water uptake at equilibrium, k is a constant related to the structure of the network, and the diffusional exponent n is a number to determine the type of diffusion. It is possible to get information about transport mechanism by determining the diffusional exponent, n. A comparison of transport types according to diffusional exponent, n is given in Table 3.1. While n = 0.5 represents the perfect Fickian diffusion, it is possible to record the n values much below 0.5 which is called Less Fickian behaviour as Fickian diffusion [90].

Table 3.1 : Transport mechanisms and diffusional exponents for hydrogel slabs [91].

Type of transport	Diffusional Exponent(n)	Time Dependence
Fickian diffusion	0.5	$t^{1/2}$
Anomalous transport	$0.5 < n < 1$	t^{n-1}
Case II transport	1	Time independent

Yanfeng and Min [26] studied swelling kinetics and responsive properties of poly(DMAEMA) hydrogels synthesized by UV-irradiation. The swelling process in a phosphate and citrate buffer solution was found to be non-Fickian. As pH was increased, the swelling process would tend to be Fickian kinetics. The hydrogel proved to be pH-sensitive at about pH 3 and the LCST in water is about 40°C. Lesho and Sheppard [40] examined the swelling and deswelling kinetics of pH-responsive crosslinked copolymers of HEMA with up to 20 mol% DMAEMA by measuring

electrical conductivity. The agreement between swelling data and buffer-mediated diffusion-reaction theory indicated that diffusive transport of protons within the hydrogel is the rate-limiting step during a pH-induced change in hydration.

The release profiles of amphiphilic hydrogels containing HEMA, DMAEMA, and a third methacrylatebased monomer 3-(trimethoxy-silyl) propyl methacrylate were investigated with respect to variation in the pH, DMAEMA content, and the crosslink density. It was reported that the gels exhibit classical Fickian diffusion release profiles and the diffusion coefficient of insulin decreased as the crosslinker tetraethyleneglycol diacrylate (TEGDA) content increased from 3 to 15 mol % [92]. The bioadhesive properties of the hydrophobic, basic polyelectrolyte hydrogel disks containing crosslinked *N*,*N*dimethylaminoethyl methacrylate-co-methyl methacrylate 30/70 mol% were evaluated in vitro using gastric (pH 1.2), sublingual (pH 6.5), vaginal (pH 4.0) and intestinal (pH 7.5) pig's mucosas [93]. It was found an increase in the adhesive strength with the increase of crosslinker content in the pH range of 4.0-7.5. For the evaluation at pH 1.2 (gastric mucosa) the opposite behavior was observed. Further experiments show that these gels present pHdepending drug release with nearly zero-order kinetics. The rate of release is highly correlated with the rate of gel swelling.

4. MECHANICAL PROPERTIES OF HYDROGELS

4.1 Elasticity of Polymer Networks

Numerous attempts have been made to describe the relation between the elastic modulus and the molecular structure. The understanding of the polymer network elasticity began in the early 1930s. The forms of the stress-strain relationships were developed beginning in 1942 with Wall[94], Treloar[77], Flory-Rehner[76], and James-Guth[95].

Rubber resembles a solid, but behaves as a liquid in that the volume stays essentially constant as it undergoes isothermal deformation. Thus, the rubber is a good example of a polymer network. It can be described as a giant network molecule made by a crosslinking reaction between the polymers. The rubberlike elasticity of the polymer networks refers to two aspects: very high deformability and essentially complete recoverability. The crosslinked materials can undergo large deformations under tension without rupturing. When the deforming force is removed, they spontaneously recover their original dimensions[96].

4.2 Theory of Rubber Elasticity

Theories on rubber elasticity can be mainly divided into two categories; one based on statistical mechanics (classical and modern molecular based theories) and the other based on continuum mechanics.

i. The classical molecular based theories describe rubber elasticity of networks in simple and idealized ways and include the affine network theory and the phantom network theory. The modern molecular based theories consider the contribution of entanglements of polymer chains to the rubber elasticity and include the constrained junction model, the slip-link model and the tube model[95-101].

ii. Continuum mechanics based theories are built on the mathematical arguments regarding strain matrix invariant of a rubber under deformation.

The network models used in this thesis to describe the elasticity of the polymer networks correspond essentially to the affine and phantom network model. In the following section, these theories will be described and a comparison will be done between two network models.

4.2.1 Affine and Phantom Network Theories

The affine and phantom network theories are the two fundamental network models which relate the molecular structure and the macroscopic strain-stress. The both models are based on mean-field approaches in which the anology between the elastic properties of an ideal, gaussian chain and a classical elastic spring is used to calculate the network free energy.

These models share some common premises in idealizing a real polymer network:

1- The intermolecular interactions between network chains are independent of the configurations of these chains.

2- The chains are Gaussian, freely joined and volumeless.

3- The total number of configurations of an isotropic network is the product of the number of configurations of the individual chains.

The main assumption of the affine network theory is that the crosslink junction points move affinely with macroscopic deformation. In an affine network, diffusion of the junctions about their mean positions is restricted by the neighboring chains sharing the same region of space. With this assumption, the fluctuation of the crosslink junctions in the networks is suppressed. The other simple assumption is that the chain segments of the network deform independently and on a microscopic scale in the same way as the whole sample. The crosslinks are assumed to be fixed in space at positions exactly defined by the specimen deformation ratio[76,77,94].

The phantom network theory is different from the affine network theory in that, the junctions of the network chains can move freely and the chains can pass through each other like phantoms. Figure 4.1 shows schematically the difference between the affine and phantom network models. In the affine network model, the crosslink points are embedded in the network have a specified fixed position. However, the junction points of the phantom network are allowed to fluctuate about their mean values (shown in Figure 4.1 by the points marked with an A)[98,99].

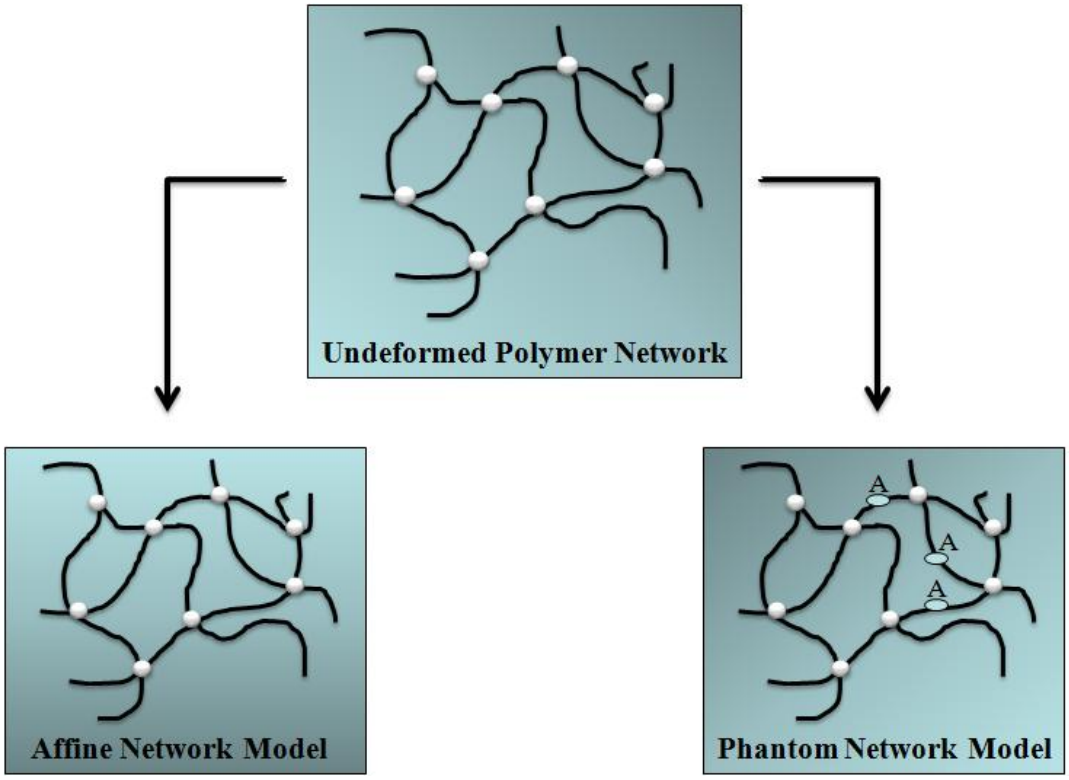

Figure 4.1 : Schematical representation of the deformation of a network according to the affine network model and the phantom network model.

4.3 Parameters Affecting Elastic Modulus of Hydrogels

When the polymer chains are chemically linked together to form a three-dimensional polymer network, the resulting material exhibits a unique set of elastic properties. If this polymer network is subjected to an external force, it undergoes elastic deformation which is dependent on its chemical composition and topology. The influence of the network structure on the elastic behavior is reflected principally through the macroscopic elastic modulus. In the next paragraphs, the elastic behavior of the polymer network is summarized in terms of the several factors.

i. Network structure: The stiffness of the polymer backbone of the gels affect the elastic modulus. A gel consist of stiff network chains due to the bulky side groups is expected to have higher elastic modulus than a flexible polymer[102]. Moreover, according to Equations (5.7) and (5.8), for usual tetrafunctional polymer networks, the elastic modulus of an affine network is twice as larger as the one for a corresponding phantom network with the same crosslink density and prepared under similar conditions.

ii. The initial monomer concentration: As the monomer concentration is increased, the effective crosslink density ν_e of the hydrogels also increases due to the more efficient consumption of the crosslinker in concentrated monomer solutions, so that the elastic modulus of gels becomes larger. In order to quantify the dependence of the effective crosslink density of gels on the monomer concentration ν_2^0, a statistical model was proposed by Bromberg et al. In this model, the gel growth process during polymerization was considered as a set of random walks of the growing radicals[103].

iii. The crosslinker concentration, i.e. the crosslinker ratio X: The elastic modulus of gels sensitively depends on the crosslinker concentration. The modulus of gels increases with increasing crosslinker concentration due to decreasing chain length between successive crosslinks.

iv. Ionic group concentration: The elastic modulus of gels after their preparation first increases with increasing charge density but then decreases continuously. The results indicate two opposite effects of charged groups: Formation of multiplets in the gel increases the elastic modulus of ionic hydrogels, whereas the effect of the electrostatic interaction of charged groups on elastic free energy decreases the modulus[104,105].

v. Swelling: The modulus of gels decreases with increasing degree of swelling. The swelling process reduces the polymer network concentration, i.e. for swollen hydrogels $\nu_2 < \nu_2^0$. According to Equation (5.8), the elastic modulus after equilibrium swelling G is usually lower than that of after preparation G_0[106].

vi. Entanglements: The constrained junction theory as well as the slip-link model have been predicted that the modulus may increase due to the presence of entanglements. The decrease of the modulus with elongation can be interpreted as a result of relaxation of entanglement constraints due to the deformation[100,101].

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5. EXPERIMENTAL

5.1 Materials

The materials used in the preparation of the hydrogels are described in this section and the chemical structure of the materials are shown in Figure 5.1.

i. **N,N-dimethylaminoethyl methacrylate (DMAEMA, Merck**): It was used as main monomer in the polymerization reactions as received. Its molecular weight is 157.22 g/mol and it has a density of 0.930 g/ml at 20°C.

ii. **2-Hydroxyethyl methacrylate (HEMA, Fluka):** It was used as comonomer in the polymerization reactions and used as received. Its molecular weight is 130.15 g/mol with a density of 1.071 g/ml at 20°C.

iii. **Diethylene glycol dimethacrylate (DEGDMA, Aldrich):** It was used as crosslinking agent and used as received. It has a density of 1.082 g/ml and its flash point is 113 °C. Its molecular weight is 242.27 g/mol.

iv. **Ammonium persulfate (APS, Merck):** It was used as an initiator in the polymerization reactions and used as received. Its molecular weight is 228.20 g/mol. It has a melting point of 120 ºC.

v. **N,N,N',N'-tetramethylethylenediamine (TEMED, Merck):** It was used as an accelerator in the polymerization reactions and used as received. It has a boiling point of 120-122 ºC. Its molecular weight is 116.21 g/mol.

vi. **Buffer solutions:** Hydrochloric acid (HCL, Merck), Potassium dihydrogen phosphate (KH_2PO_4, Riedel-de Haen), Potassium phosphate (K_3PO_4, J.T.Baker) and Sodium monohydrogen phosphate (Na_2HPO_4, Merck) were used to prepare buffer solutions with different pH values.

vii. **Ionic salt solutions:** Sodium chloride (NaCl, Merck), Potassium chloride (KCl, Merck), Potassium bromide (KBr, Merck), Potassium iodide (KI, Carlo Erba) as monovalent salts , Calcium chloride ($CaCl_2$, J.T.Baker), Magnessium chloride

($MgCl_2$, J.T.Baker) and Barium chloride ($BaCl_2$, Merck) as divalent salts are used to prepare salt solutions that have different ionic strengths.

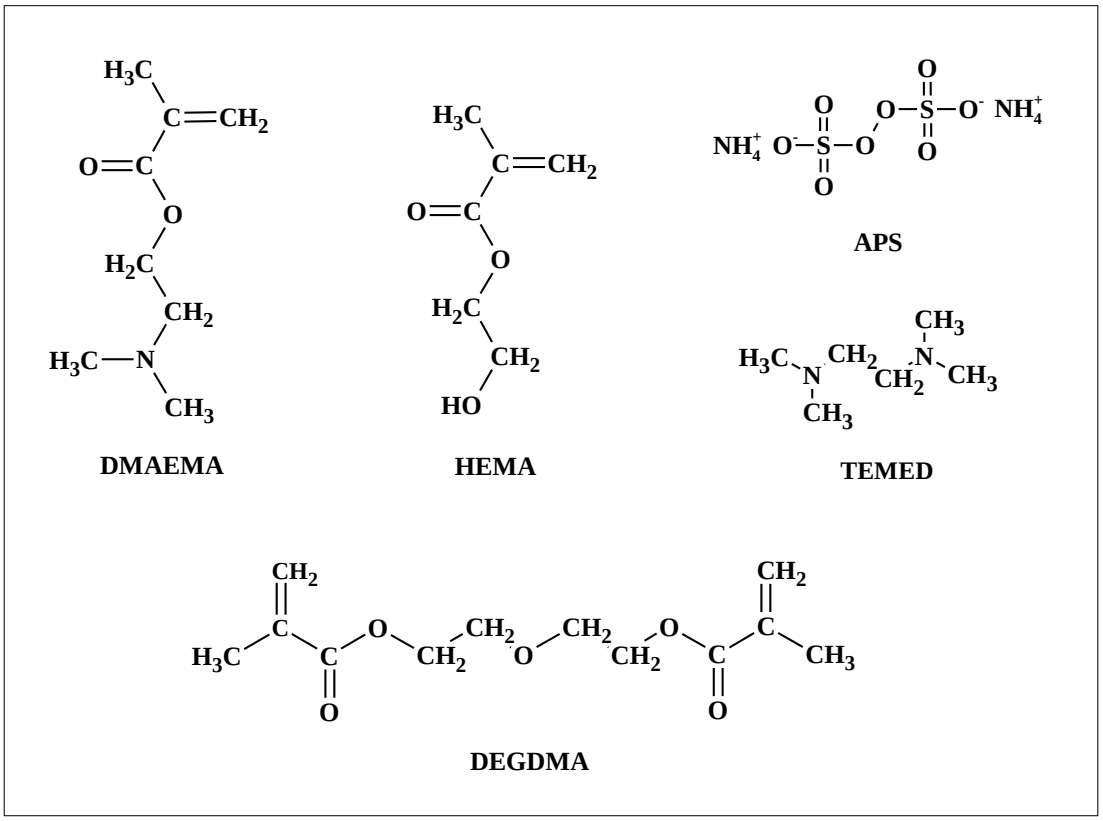

Figure 5.1 : The materials used in the preparation of the hydrogels.

5.2 Experiment Equipments

a. Electronic Digital Compass: The diameters of the cylindrical gel samples were measured using a calibrated digital compass (Mitutoyo). The device has a measuring range between 0-150 mm with an accuracy ± 0.02 mm.

b. Heating Oven: The oven (Binder ED53) is used for the swelling experiments. It runs in the range of 5 - 300 °C with a sensitivity of 1 °C.

c. Analytical Balance: For the weighing measurements an analytical balance (AND GR-200) with a sensitivity of 0.0001 g is used. Its weighing capacity is 210 g.

d. Temperature Controller: This aparatus (Stuart SCT1) is used for kinetic experiments. Its temperature range 20 to 200 °C with an accuracy of ±0.5 °C.

e. Sterile Syringes: Gelation process is conducted in 1 ml/cc sterile insuline syringes (Beybi). Inner diameter of syringe is 4.6-4.8 mm.

f. Uniaxial Compression Apparatus: In order to measure the elastic modulus of gels, a home-made uniaxial compression apparatus was used as shown in the Figure 5.2.

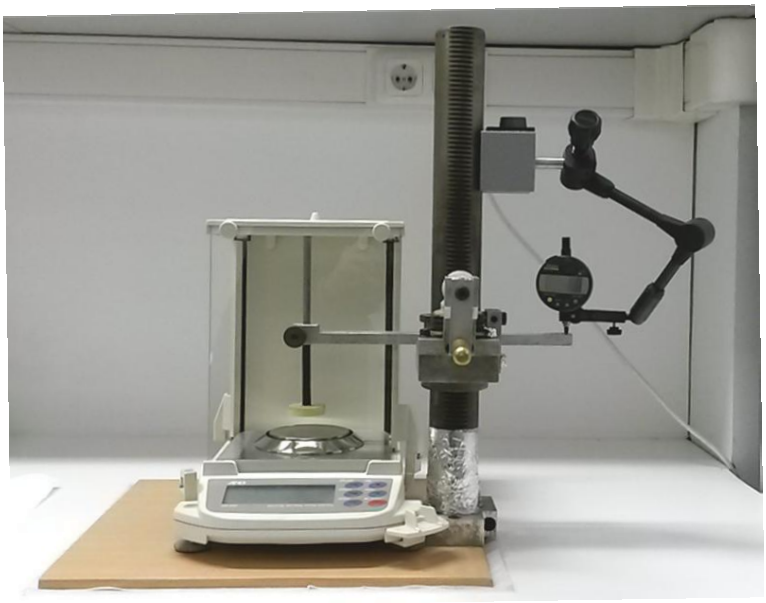

Figure 5.2 : Schematic view of uniaxial compression aparatus.

5.3 Experimental Method

The experimental work of this thesis can be expressed by three main parts:

1) Synthesis of P(DMAEMA-co-HEMA) hydrogels and determination of the optimum synthesis parameters:
    a) Synthesis of P(DMAEMA-co-HEMA) copolymeric hydrogels with different HEMA concentrations by using DEGDMA as crosslinker at room temperature.
    b) Gravimetric measurements to determine the gel fraction, the polymer network concentration at the stage of gel preparation and the monomer conversion.
2) Swelling experiments:
    a) Determination of the swelling capacity of hydrogels in;
        i) Pure water,
        ii) Buffer solutions with different pH values,
        iii) Monovalent and divalent salt solutions having different ionic strength.

b) Investigation of swelling/deswelling kinetic of hydrogels and calculation of diffusion coefficient for water.

3) Mechanical measurements:

a) Evaluation of elastic modulus of hydrogels both after their preparation and at equilibrium swollen state by the uniaxial compression measurements.

b) Determination of mechanical behavior of hydrogels by using rubber elasticity theory.

5.4 Synthesis of P(DMAEMA-co-HEMA) Hydrogels

The hydrogels were synthesized by copolymerizing DMAEMA as the primary monomer, HEMA as the comonomer, and DEGDMA as the crosslinker in an aqueous solution. The preparation was carried out at 21 ± 0.2 ^{o}C by free-radical crosslinking copolymerization which is illustrated schematically in Figure 5.3. The redox initiator system consisting of 2.63 mM APS - 0.375 v/v % TEMED was used to initiate the polymerization. APS and TEMED stock solutions were prepared by dissolving 0.080 g APS and 0.375 mL TEMED separately in 10 mL of water.

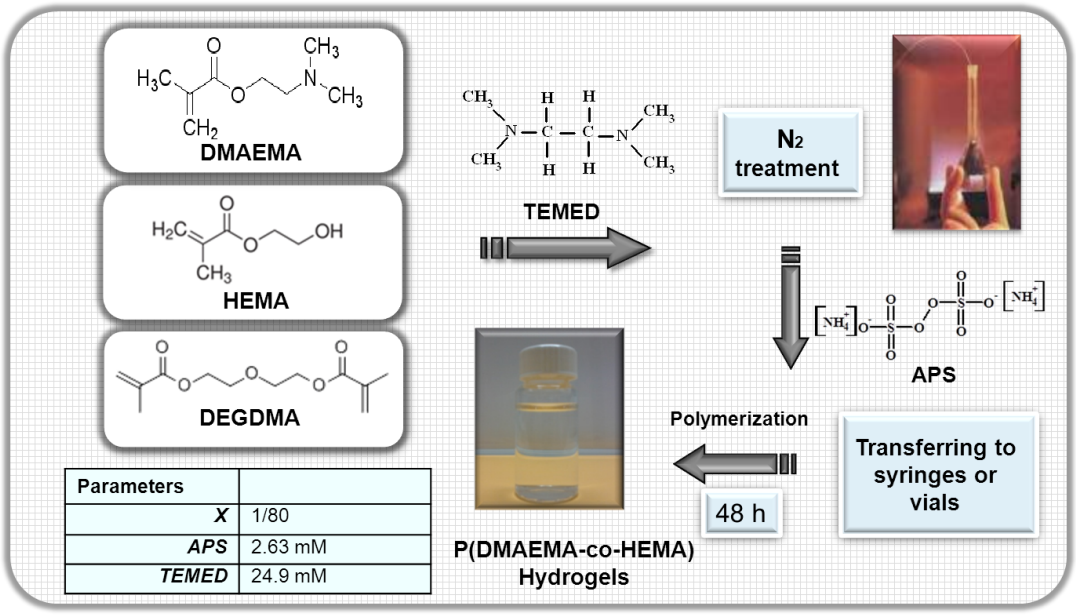

Figure 5.3 : Formation steps of P(DMAEMA-co-HEMA) hydrogels by free-radical crosslinking copolymerization.

Both the crosslinker ratio (mole ratio of the crosslinker DEGDMA to the monomers DMAEMA and HEMA) and the total monomer concentration were fixed at 1/80 and

33 w/v%, respectively, whereas the HEMA content of the monomer mixture was varied from 0 to 100 mol%. The synthesis conditions for the copolymeric hydrogels are listed in Table 5.1 and a typical procedure for the synthesis of the hydrogel with 10 mol% HEMA in the monomer feed composition is described as follows: DMAEMA (3.225 mL), HEMA (0.270 mL), DEGDMA (0.060 mL) and TEMED stock solution (1.0 mL) were mixed in a graduated flask. After bubbling nitrogen for 20 minutes in order to eliminate oxygen, APS stock solution (1.0 mL) was added and after shaking the flask, the solution was poured into several syringes. Then, the polymerization reaction was conducted at 21 ± 0.2 ^{o}C for 48 h.

Table 5.1 : The synthesis conditions of the copolymeric hydrogels.

Parameters	Values
Total monomer concentration, C_0	33 w/v %
Crosslinker ratio *X* (mole ratio of the crosslinker DEGDMA to the monomers DMAEMA and HEMA)	1/80
Initiator (APS) concentration	2.63 mM APS
Accelerator (TEMED) concentration	24.9 mM (0.375 v/v %)
Polymerization media	Water
Reaction time	48 h

In this study, hydrogels were synthesized by free-radical copolymerization method which is a commonly used method for polymerization of monovinyl monomers in the presence of a bifunctional crosslinker and solvent. Probable reaction mechanism of P(DMAEMA-co-HEMA) hydrogels using APS-TEMED as redox initiator system and DEGDMA as crosslinker is given in Figure 5.4.

5.5 Characterization of P(DMAEMA-co-HEMA) Hydrogels

5.5.1 Polymer Network Concentration at The Stage of Gel Preparation

All the hydrogel samples after preparation were subjected to the gravimetric tests to determine the monomer conversions and the gel fractions. The mechanical properties and the swelling behavior of hydrogels sensitively depend on the degree of dilution at which they are formed. The degree of dilution of the networks after their preparation was denoted by $\nu_2{}^{\circ}$, the volume fraction of crosslinked polymer after the gel preparation. In order to determine $\nu_2{}^{\circ}$, the hydrogels after preparation were first swollen in water to extract non-polymerizable or soluble components and then the

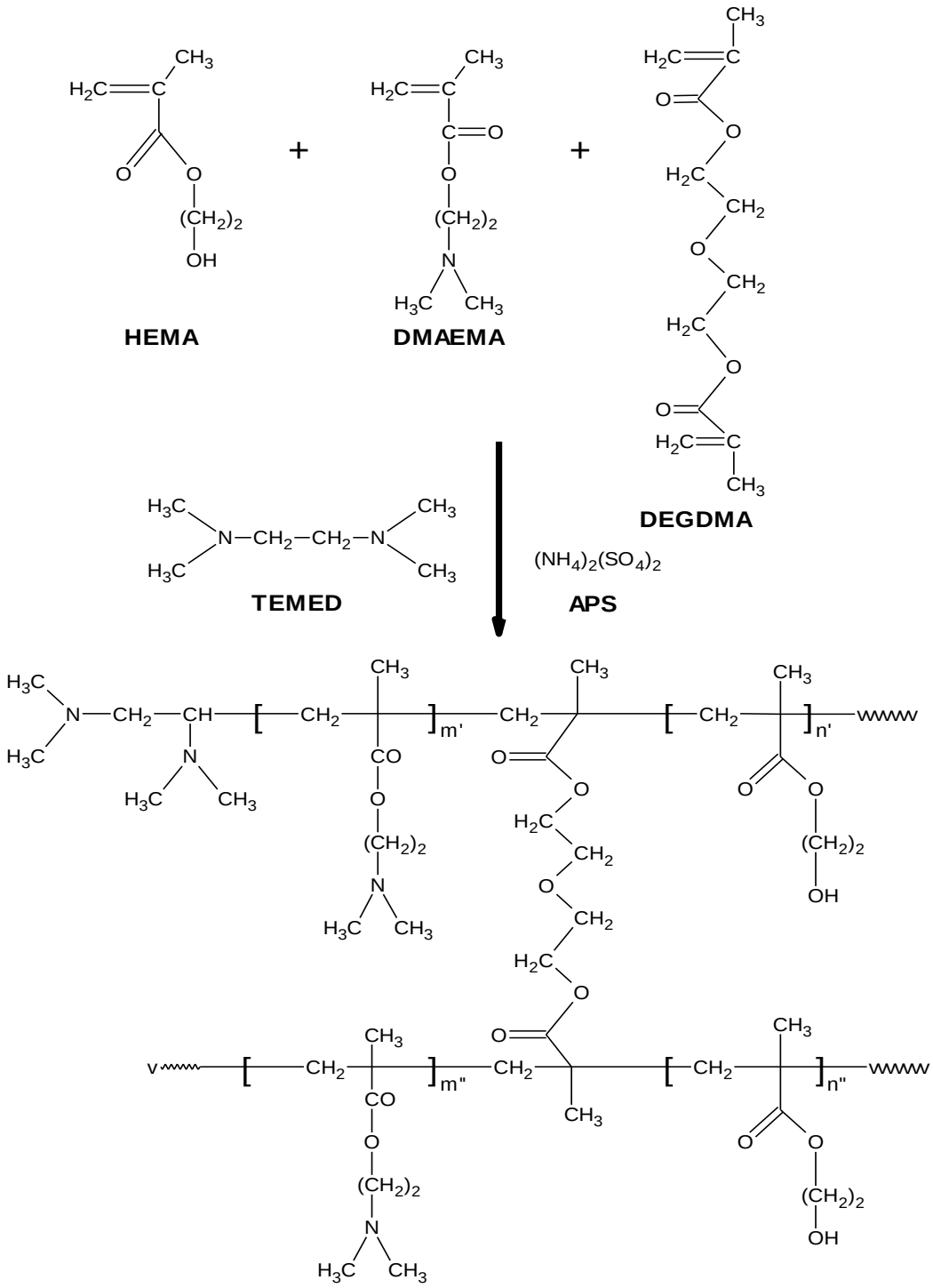

Figure 5.4 : Free-radical copolymerization reaction mechanism of P(DMAEMA-co-HEMA) hydrogels.

swollen hydrogels were dried at room temperature to the constant weight. In Figure 5.5 photographs of a gel sample after preparation, after swelling and then after drying process are shown. The experimental values of $\nu_2°$ were calculated using the Equation (3.12). Moreover, assuming that the monomer conversions were complete

after the crosslinking copolymerization, the theoretical values of ν_2° were also calculated using the Equation (3.11).

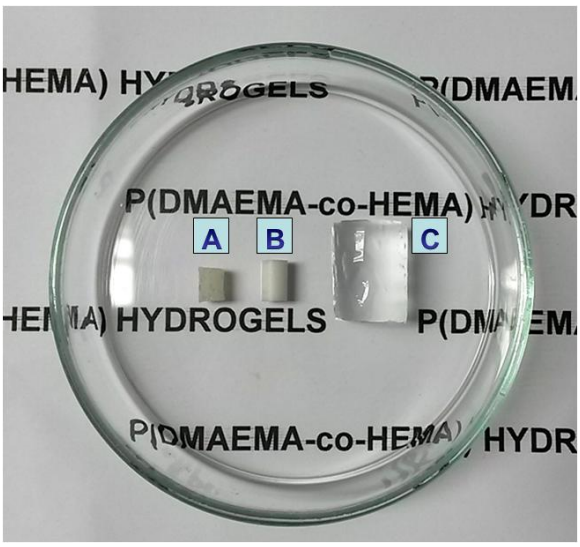

Figure 5.5 : Photographs of the gel samples after drying (A), after preparation (B) and after equilibrium swelling (C).

5.5.2 Swelling Measurements

The swelling behaviors of the hydrogels were investigated in water, in buffer solution as well as in aqueous salt solutions. After the crosslinking polymerization, the hydrogels were cut into samples of about 8 mm length and then the initial weight and diameters of the gel samples were measured. The gel samples were immersed in an excess of distilled water for at least two weeks to reach the swelling equilibrium at room temperature. The water of the gel samples were replaced during swelling process in order to remove the unreacted species. The samples were weighed and swollen diameters were measured at swelling.

The volumetric and gravimetric techniques were used to measure the swelling ratios of the hydrogels. As part of volumetric measurements, the equilibrium swelling was quantified using the equilibrium volume swelling ratio of copolymeric hydrogels V_{eq} and calculated by using Equation (3.8). The volume fraction of crosslinked polymer in the equilibrium swollen gel $\nu_{2,eq}$ was calculated as:

$$\nu_2 = \frac{\nu_2^o}{V_{eq}} \qquad \textbf{(5.1)}$$

In gravimetric measurements, the weight of the gel samples after preparation (m_o) and after swelling (m_{sw}) were measured by the electronic balance.

5.5.2.1 pH-dependent swelling experiments

The equilibrium swelling measurements of P(DMAEMA-co-HEMA) gels were carried out in buffer solutions ranging pH from 2.1 to 11.2 at room temperature. For the swelling studies, the gel samples taken from the same gel were immersed in an excess of the solutions for at least two weeks to reach the equilibrium swelling at a desired temperature. Then, by using the volumetric techniques, the equilibrium swelling of PDMAEMA gels was tested by measuring the diameters by a calibrated digital compass (Mitutoyo). Four measurements were carried out on each gel sample to achieve good precision and the equilibrium volume swelling ratio of copolymeric hydrogels V_{eq} (volume of equilibrium swollen hydrogel / volume of the hydrogel just after preparation) which was calculated according to Equation (3.8). Then, the volume fraction of crosslinked polymer in the equilibrium swollen hydrogel v_2 was calculated using the Equation (5.1). In Figure 5.6, the chemical structures of the monomers employed for the preparation of the corresponding P(DMAEMA-co-HEMA) copolymeric hydrogels were represented. Figure 5.6 also schematizes the response to the pH variation of the surrounding medium of PDMAEMA gel consisting of basic polymer chains. Above the pKa, the basic groups are in a nonionized state and the hydrogel particles possess a certain volume. Below the pKa, the increase in pH is accompanied by an increase in volume of the hydrogel network, resulting from the generation of negative charges along the polymer network [25].

5.5.2.2 Temperature dependent swelling experiments

The temperature dependence of the equilibrium swelling ratio of the P(DMAEMA-co-HEMA) hydrogels in water as well as in pH buffer solutions was studied from 25 to 75 ^{o}C. The sample was immersed in the solution to swell for 3 days at each predetermined temperature, after which the sample was taken out and weighed and measured the swollen diameter after blotting the excess in the solution on the surface by filter paper. The hydrogel sample was then equilibrated in distilled water at another predetermined temperature using the same method as above. The equilibrium

volume swelling ratio of copolymeric hydrogels V_{eq} at each temperature was calculated according to Equation (3.8).

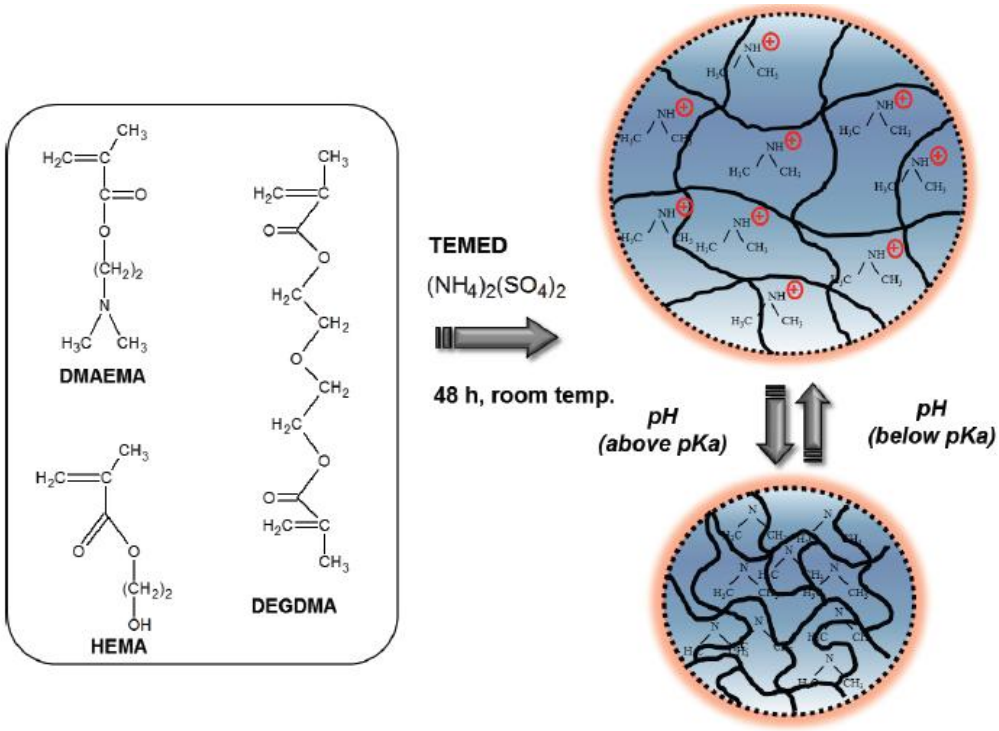

Figure 5.6 : Synthetic conditions for the preparation of P(DMAEMA-co-HEMA) hydrogels and schematic illustration of the variation in dimension of PDMAEMA gel consisting of basic polymer chains.

5.5.2.3 Dynamic swelling/deswelling experiments

For dynamic swelling measurements, the dried sample was placed in buffer solution of pH 2.1 as well as aqeous salt solutions of 10^{-5} M at room temperature and the swollen hydrogels removed from the solution at regular intervals were dried with filter paper, weighed and placed again. The measurements were continued until a constant weight was reached for the sample and the amount of water absorbency was monitored gravimetrically. The water uptake at time *t* was defined as follows:

$$WU(t) = \frac{w_t - w_d}{w_d} \qquad \textbf{(5.2)}$$

where w_t is the weight of the wet copolymer hydrogel sample at time t and w_d is the weight of dry hydrogel. The deswelling kinetics of the hydrogel was studied by transferring the swollen hydrogel samples into buffer solution of pH 8.0 as well as into aqueous solution of 1.0 M. At predetermined time intervals, the hydrogel sample

was taken out from the hot solution and weighed after blotting excess water on the surface by filter paper. The water retention was defined as follows:

$$WR(t) = \frac{w_t - w_d}{w_s - w_d} \tag{5.3}$$

here w_s is the weight of the swollen hydrogel at equilibrium and the other symbol is the same as defined above. The equilibrium swelling ratio, SR_{eq}, is defined as follows:

$$SR_{eq} = \frac{w_s - w_d}{w_d} \tag{5.4}$$

5.5.3 Mechanical Measurements

The uniaxial compression measurements were performed on the hydrogels after their preparation and at their swelling equilibrium in water, in buffer solutions as well as in aqueous salt solutions. A cylindrical gel sample of 4.6-4.8 mm in diameter and 7 mm in length was placed on a digital electronic balance (AND GR-200, readability and reproducibility: 0.1 mg). A load was transmitted vertically to the gel through a rod fitted with a PTFE (Teflon) end-plate. The force acting on the gel F was calculated from the reading of the balance m as F=mg, where g is gravitational acceleration (g = 9.8030 m.s-2). The resulting deformation $\Delta l = l_o - l$, where l and l_o are the initial undeformed and deformed lengths, respectively, was measured using a digital comparator (IDC type Digimatic Indicator 543-262, Mitutoyo) which was sensitive to displacements of 10^{-3} mm. The force and resulting deformation were recorded after 10 sec of relaxation. The measurements were conducted up to about 20% compression. From the repeated measurements, the standard deviations in the modulus value were less than 3%. The deformation ratio α (deformed length/initial length) was calculated as:

$$\alpha = 1 - \frac{\Delta l}{l_0} \tag{5.5}$$

The corresponding stress f was calculated as f = F / A, where A is the cross-sectional area of the specimen, $A = \pi D_0 / 2$, where D_o is its initial diameter. For uniaxial

deformation, the statistical theories of rubber elasticity yield for Gaussian chains an equation of the form:

$$f = G\left(\alpha - \alpha^{-2}\right) \tag{5.6}$$

where the elastic modulus of the gel sample G is given by the following equation [76].

$$G = A\,\nu_e RT\left(\nu_2^0\right)^{2/3}\left(\nu_2\right)^{1/3} \tag{5.7}$$

where A is the front factor that equals to 1 for an affine network and 1- (2 / ϕ) for a phantom network, in which ϕ is the functionality of the crosslinks, ν_e is the effective crosslink density, R and T are in their usual meanings.

For the hydrogels after their preparation, $\nu_2 = \nu_2^0$ and then the modulus after preparation G_0 is given by:

$$G_0 = A\nu_e RT\nu_2^0 \tag{5.8}$$

The compressive moduli of hydrogels were calculated from the average slope of the initial linear portion (5% strain) of the stress vs. strain curve using Equation (5.6). At least four independent samples were tested for each set of hydrogels and the standard deviations in the modulus value were less than 3%.

The effective crosslink density ν_e is defined as the concentration of the elastically active chains. The number of segments between two successive crosslinks N and the molecular weight of network chain $\overline{M}_c$ are related to the crosslink density ν_e through the equation:

$$\nu_e = \frac{\rho}{\overline{M}_c} = \frac{1}{N.\overline{V}_1} \tag{5.9}$$

where V_1 is the molar volume of solvent and N also gives the average network chain length.

6. RESULTS AND DISCUSSION

The main aim of this thesis was to design and prepare a series of cationic copolymeric hydrogels based on DMAEMA and HEMA that would provide improved mechanical properties within their network structure for use in bioengineering applications. For this purpose, the swelling behavior and physico-mechanical properties of resulting hydrogels were studied as a function of the comonomer concentration, the pH of the swelling medium, the presence of different type of salts and the temperature. In this section;

i. The swelling behavior of P(DMAEMA-co-HEMA) copolymeric hydrogels in water, in buffer solutions as well as in aqueous salt solutions were discussed.

ii. The pH-dependent volume transition of P(DMAEMA-co-HEMA) copolymeric hydrogels were discussed as a function of the comonomer HEMA concentration used in the preparation and the temperature.

iii. The elastic behavior of P(DMAEMA-co-HEMA) copolymeric hydrogels both after preparation and after equilibrium swelling in water, in buffer solutions as well as in aqueous salt solutions were discussed.

6.1 P(DMAEMA-co-HEMA) Copolymeric Hydrogels In Water

A series of copolymeric hydrogels based on DMAEMA as the primary monomer, HEMA as the comonomer was prepared throughout this study. The selection of DMAEMA as the starting monomer is due to the fact that PDMAEMA itself exhibits dual pH and temperature responsiveness. The nature of the thermo-responsive behavior is the balance of hydrophobicity and hydrophilicity of PDMAEMA, while the pH-sensitive behavior is due to the existence of tertiary amino-group, which becomes protonated with the decrease of pH of the aqueous medium. These properties of PDMAEMA were used to develop copolymeric hydrogels with good comprehensive properties including mechanical properties through copolymerization

of DMAEMA with a biocompatible co-monomer HEMA which also contains pendant hydroxyl functionalities. In the following, the equilibrium swelling behavior and the elasticity of P(DMAEMA-co-HEMA) hydrogels in water will be discussed as a function of the comonomer HEMA concentration and the temperature.

6.1.1 Swelling of P(DMAEMA-co-HEMA) hydrogels in water

The hydrogels were prepared by free-radical crosslinking copolymerization reactions of main monomer DMAEMA, the comonomer HEMA in the presence of DEGDMA as crosslinker. Ammonium persulfate - *N,N,N',N'*-tetramethylethylenediamine (APS-TEMED) redox initiator system was used to initiate the polymerization reactions. To make comparison, homopolymeric PDMAEMA and PHEMA hydrogels were also prepared under the same experimental condition.

All the hydrogel samples after preparation were subjected to the gravimetric tests to determine the monomer conversions and the gel fractions. The swelling capacity and the mechanical properties of gels sensitively depend on the degree of dilution at which they are formed. The presence of water during the gel formation process is known to produce supercoiled polymer chains in the dry state so that the increase of their dimensions during swelling does not require much loss of their conformational entropy. The degree of dilution of the networks after their preparation denoted by ν_2^0 is also known as the volume fraction of crosslinked polymer after the gel preparation and was experimentally determined using Equation (3.12). By assuming that the monomer conversion is complete after the crosslinking, the theoretical values of ν_2^0 were calculated from the initial molar concentration of the monomers C_0 using the Equation (3.11). In Figure 6.1, the experimental and theoretical values ν_2^0 of P(DMAEMA-co-HEMA) copolymer hydrogels were plotted against the comonomer HEMA content in the network. It was observed that ν_2^0 values decrease slightly with increasing comonomer composition.

P(DMAEMA-co-HEMA) copolymeric hydrogels formed at various HEMA concentrations were subjected to the swelling measurements in water. The measurements were carried out at room temperature (24 ± 0.5°C). The equilibrium swelling ratio of hydrogels was determined by measuring the diameter of the hydrogel samples after equilibrium swelling in water D and after synthesis D_0 by a

calibrated digital compass. The volume fraction of the crosslinked polymer in the equilibrium swollen gel ν_2 and the normalized volume of the equilibrium swollen hydrogels V_{eq} (volume of equilibrium swollen gel/volume of the gel just after preparation) were also calculated using Equations (3.7) and (3.8), respectively.

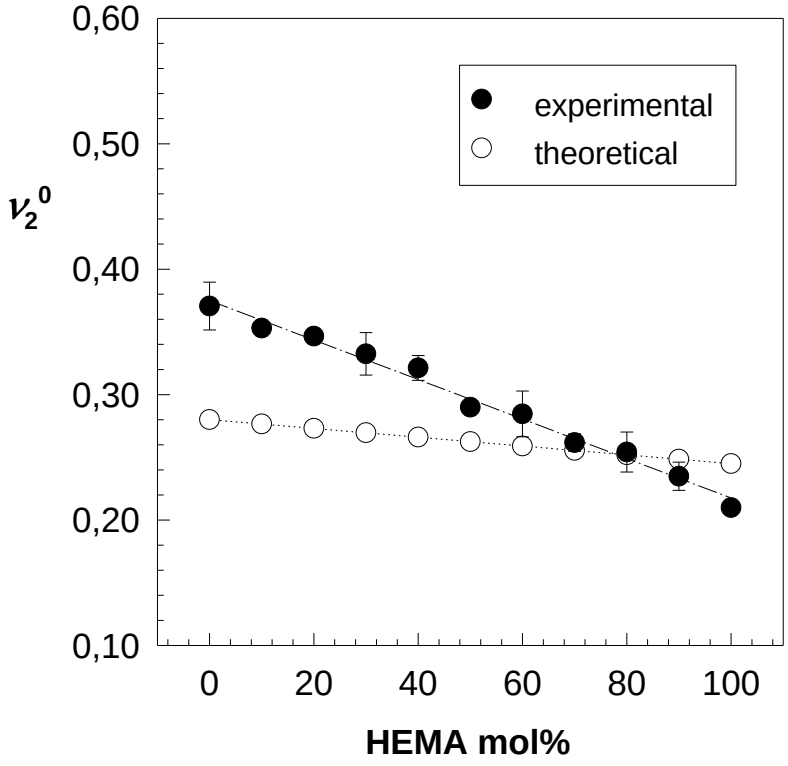

Figure 6.1 : Experimental and theoretical values ν_2^0 of P(DMAEMA-co-HEMA) copolymeric hydrogels shown as a function of the HEMA mol%.

The understanding of the swelling ratios for P(DMAEMA-co-HEMA) hydrogels with different chemical compositions is of primary importance; more specifically, one wants to be able to predict the swelling ratio as a function of the comonomer content under several experimental conditions. The swelling ratio, which relates to the expansion of polymer network promoted by chain expansion, is mainly governed by the interaction of the polymer chains in the swelling media and rubber elasticity due to cross-linking of these polymer chains. The effect of various DMAEMA/HEMA mole ratios on the swelling of copolymeric P(DMAEMA-co-HEMA) hydrogels was studied in water and the results were collected in Figure 6.2(A). The volume fraction of crosslinked polymer in the equilibrium swollen P(DMAEMA-co-HEMA) hydrogels ν_2 was also shown as a function of the mole

fraction of HEMA in the comonomer feed in Figure 6.2(B). Among the most important quantifiable hydrogel characteristics is the polymer volume fraction in the swollen state, ν_2, which is a quantitative description of the relative amount of water imbibed into the gel based on volume.

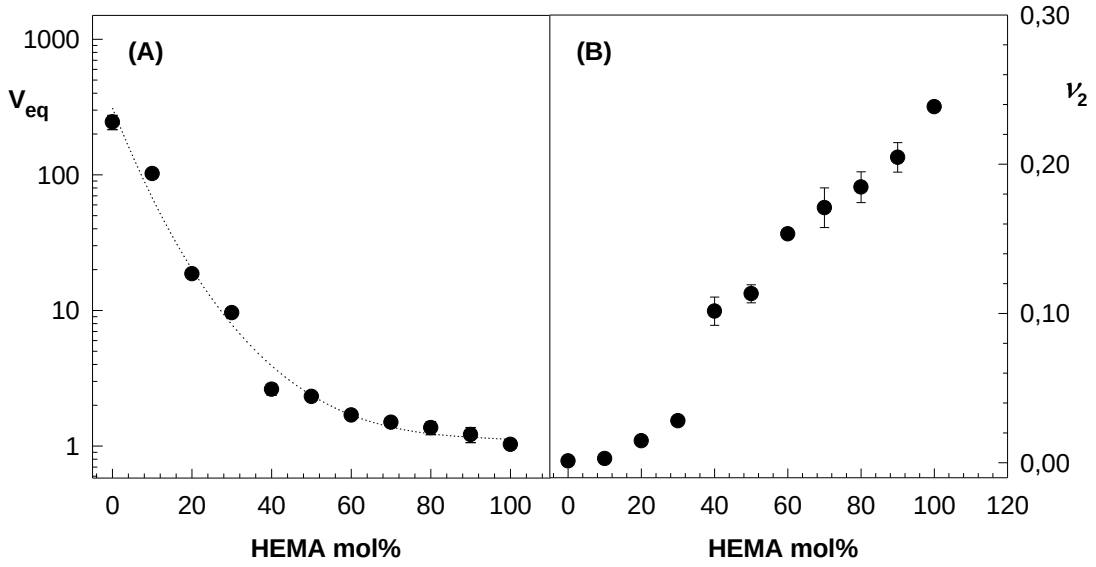

Figure 6.2 : The equilibrium volume swelling ratio of P(DMAEMA-co-HEMA) hydrogels V_{eq} (A) and the volume fraction of crosslinked polymer in the equilibrium swollen P(DMAEMA-co-HEMA) hydrogels ν_2 (B) shown as a function of the mole fraction of HEMA in the comonomer feed.

A considerable variation in the swelling capacity of copolymer P(DMAEMA-co-HEMA) hydrogels was observed when the hydrogels were modified with the comonomer HEMA. The hydrogels with higher DMAEMA content (100-70 mol-%) exhibited noticeable swelling ratios in water and were able to increase their volume 25-fold with respect to after-preparation state. In the case of DMAEMA rich comonomer hydrogels, the concentration of ionizable groups increased with increasing DMAEMA, which enhanced the extent of the swelling. The additional contribution of the osmotic pressure with increasing amount of DMAEMA causes a higher equilibrium swelling for P(DMAEMA-co-HEMA) copolymers than in homopolymeric PHEMA hydrogels. As can be seen from Figure 6.2, increasing HEMA content of the copolymer caused a gradual decrease in the swelling ratio of the resulting hydrogels. The decrease in swelling with increasing HEMA content can be related with the formation of hydrophobic domains including pendant moieties belonging to different network subchains. These domains stabilize the compact

structure of the gel, and a higher degree of ionization is required to destroy them. The hydrophobic attractions are a consequence of the presence of water near the hydrophobic moieties in aqueous solutions, and also the temperature dependence of the hydrogen bonding. A similar observation has been reported Yuk and coworkers for random copolymers of DMAEMA and ethyl acrylamide (EAAm) which exhibit LCST behavior due to the formation of hydrogen bonding between DMAEMA and EAAm residues with a hydrophobic contribution to the LCST [107].

6.1.2 Effect of temperature on the swelling behavior of P(DMAEMA-co-HEMA) hydrogels in water

Figure 6.3 shows the equilibrium swelling of P(DMAEMA-co-HEMA) hydrogels for the whole range of HEMA content investigated at selected temperatures. The figure mainly illustrates the effect of the composition and temperature on the swelling degree of resulting hydrogels. A strong temperature dependence is accounted for the copolymeric hydrogels with higher DMAEMA content. As seen, the equilibrium swelling ratio of P(DMAEMA-co-HEMA) hydrogels in water significantly decreases with increasing the comonomer HEMA content, especially in the range of HEMA content between 0 and 40 mol%. The copolymeric hydrogels containing higher DMAEMA concentrations exhibit larger equilibrium swelling ratio at low temperatures. Since the amino groups of DMAEMA in the network structure form intermolecular hydrogen bond with surrounding water at low temperature, the hydrogels extend and results in higher swelling ratio; while hydrogen bonds are overwhelmed by hydrophobic interactions among hydrophobic groups over the LCST, which cause shrinkage of the copolymer structure.

Fig.6.3 also illustrates that the temperature increment leads to lower swelling values indicating that the temperature decrease favors the uptake of water into the hydrogel structure. It means that increasing electrostatic repulsion between charged sites on DMAEMA disrupts the hydrogen bonds between HEMA and DMAEMA. Thus, the resulting P(DMAEMA-co-HEMA) hydrogels become relatively hydrophobic and expel water molecules resulting in a reduced volume swelling ratio at temperatures higher than 35°C. It was also observed that the copolymer of DMAEMA and HEMA exhibits strong thermosensitivity owing to the strengthening of the hydrophobic interactions with increasing temperature.

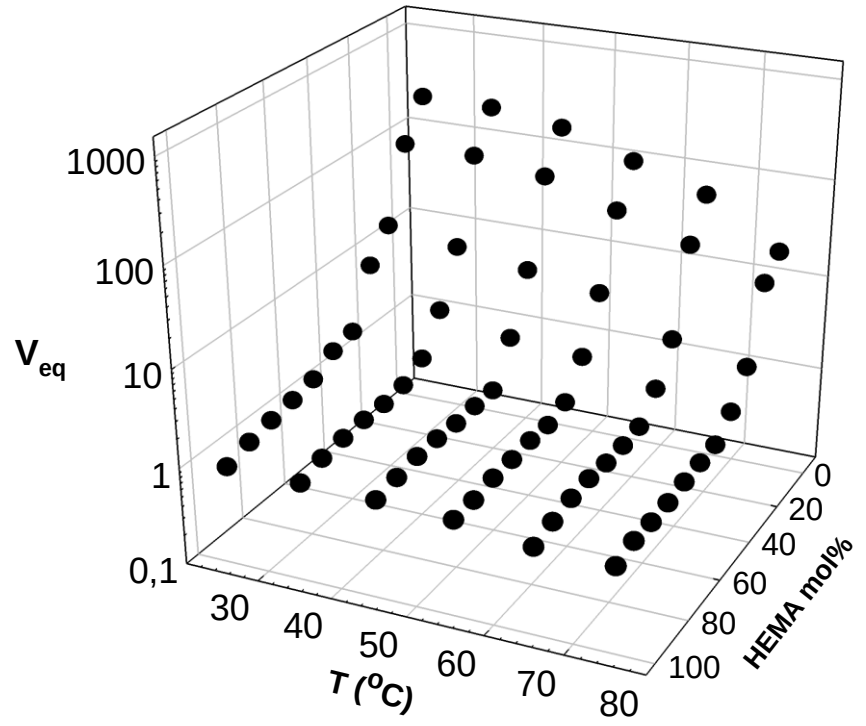

Figure 6.3 : The equilibrium volume swelling ratio of P(DMAEMA-co-HEMA copolymeric hydrogels *Veq* in water shown as a function of the temperature.

Another point observed from Fig. 6.3 was that the change in temperature had no effect on the water uptake of PHEMA hydrogels since PHEMA is a non-ionic polymer. The swelling studies showed that the incorporation of HEMA into the structure of DMAEMA changes the swelling behavior of the resulting hydrogels drastically. It was reported that PDMAEMA has a lower critical solution temperature in water which fall in the wide range of 38-50ºC [25,28,41]. For copolymer hydrogels, the swelling ratios were observed higher at lower temperatures (<LCST) and lower at higher temperatures (>LCST). This phenomenon makes the swelling ratios of the hydrogels decrease rapidly around the gel transition temperature. This can also be proved using the photographs of a P(DMAEMA-co-HEMA) hydrogel at various temperatures (Figure 6.4). The hydrogel sample, which was transparent at 25^{o}C, obtained a milky white color when the temperature was increased up to 65^{o}C. If the temperature was cooled down to 25^{o}C from 65^{o}C, the hydrogel becomes transparent again. This also confirmed the temperature responsive nature of the resulting copolymeric hydrogels.

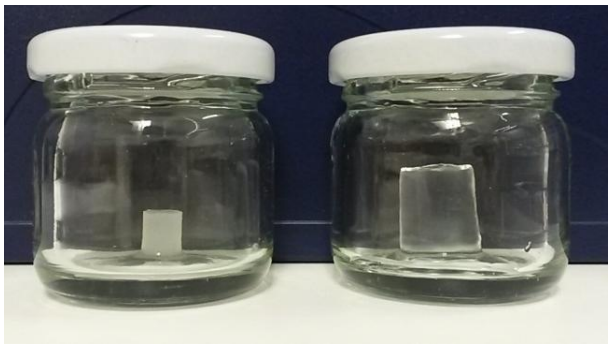

Figure 6.4 : The photographs of a P(DMAEMA-co-HEMA) hydrogel containing 20 mol% HEMA at 25^{o}C (right) and at 65^{o}C (left).

6.1.3 Elasticity of P(DMAEMA-co-HEMA) copolymeric hydrogels in water

Since the network elasticity theories describe the relationship between the gel structure and the swelling process, the mechanical properties of hydrogels are essential parameters to investigate when they are used as drug-delivery materials. For P(DMAEMA-co-HEMA) copolymeric hydrogels prepared in this study, the effect of comonomer concentration used in the preparation on the elastic and swelling properties is not well understood. When fixed charges are incorporated into the polymer network, additional complications appear regarding the description of the swelling properties. The typical stress-strain curves of P(DMAEMA-co-HEMA) copolymeric hydrogels both after preparation and after their equilibrium swelling in water were shown in Figure 6.5. It was observed that the slope of the stress-strain isoterms varies depending on the mole fraction of the comonomer HEMA used in the preparation while the chemical crosslink density of hydrogels is the same. The elastic moduli of the copolymeric hydrogels were calculated from the slope of stress-strain isotherms and the results were collected in Figure 6.6. The elastic moduli of P(DMAEMA-HEMA) copolymeric hydrogels after preparation G_0 (solid symbols) and after equilibrium swelling in water G (open symbols) were shown as a function of the comonomer HEMA content.

The elastic modulus, also known as Young's modulus, is one of the characteristics network parameters for evaluating material's stiffness which is directly proportional to the crosslinking density of the network structure. From Figure 6.6, a dramatic increase in the elastic modulus of P(DMAEMA-co-HEMA) hydrogels can be seen with increasing the mole fraction of comonomer HEMA content. The influence of comonomer HEMA content on the elasticity of P(DMAEMA-co-HEMA) hydrogels

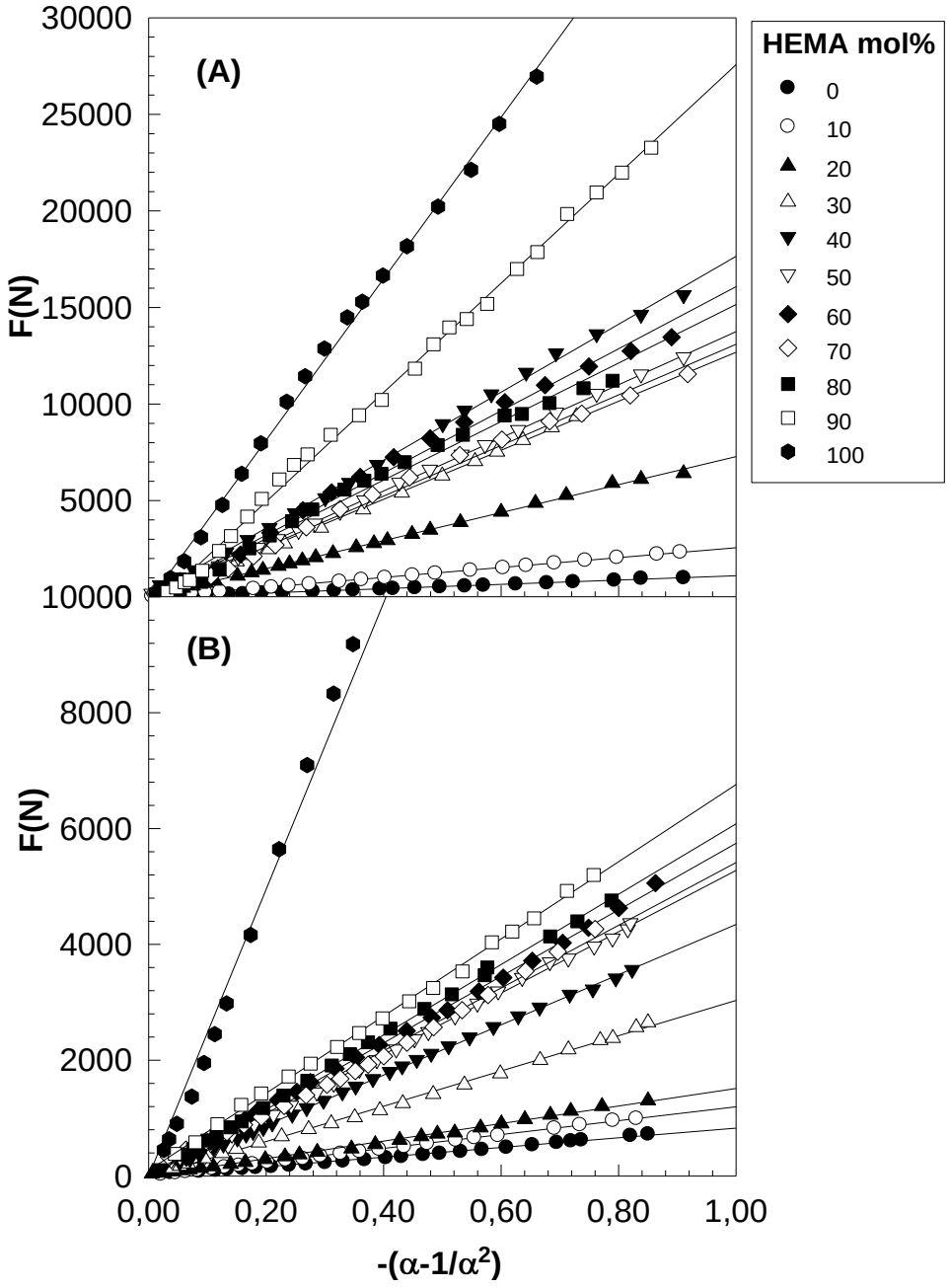

Figure 6.5 : Stress - strain isoterms of P(DMAEMA-co-HEMA) hydrogels after their preparation (A) and after equilibrium swelling in water (B). The mole fraction of comonomer HEMA is indicated in the figure.

indicated that the elastic modulus of hydrogels after equilibrium swelling in water is also lower than that of after preparation state over the entire range of HEMA concentration. As can be seen from Figure 6.2 that the lower swelling ratio caused by the augment of comonomer HEMA content indicates a higher crosslinking density, which means the polymer chains in the network matrix becomes more rigid, resulting in the improvement of elastic modulus. This can be attributed to lower water content of the more hydrophobic networks. The uniaxial compression testing results showed

that the incorporation of HEMA significantly enhanced the mechanical properties of P(DMAEMA-co-HEMA) hydrogels. It is obvious that all the P(DMAEMA-co-HEMA) copolymeric hydrogels exhibit much higher toughness than that of the corresponding pure P(DMAEMA) hydrogel.

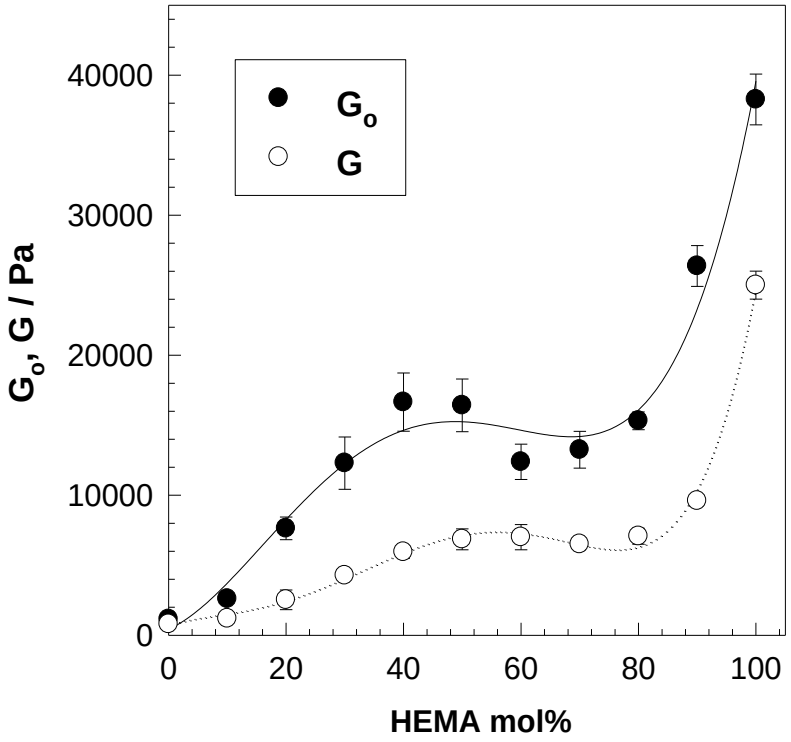

Figure 6.6 : The elastic moduli of P(DMAEMA-co-HEMA) hydrogels both after their preparation (filled symbols) and after equilibrium swelling in water (open symbols) plotted as a function of the mole fraction of HEMA in the comonomer feed.

In Figure 6.7, the photographs of swollen P(DMAEMA-co-HEMA) hydrogel sample containing 30 mol% HEMA in the feed during the uniaxial compression test also showed that the swollen P(DMAEMA-co-HEMA) hydrogels remain mechanically stable and can be compressed up to larger compression without any crack development.

The most remarkable observation from the stress–strain curves of P(DMAEMA-co-HEMA) hydrogels was that the addition of 30 mol% HEMA into the PDMAEMA network structure results in ten-fold increasing in the elastic modulus when compared with the homopolymeric PDMAEMA hydrogels. The improvement in the mechanical properties can be attributed to the ability of the comonomer HEMA to reinforce the network structure of P(DMAEMA-co-HEMA).

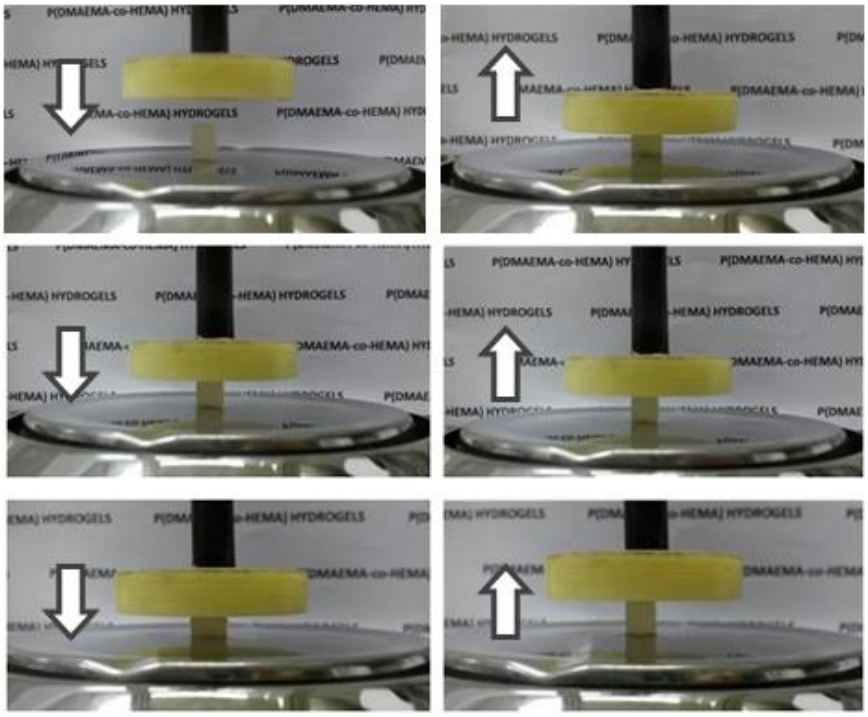

Figure 6.7 : Photographs of swollen P(DMAEMA-co-HEMA) hydrogel sample containing 30 mol% HEMA in the feed during the uniaxial compression test.

The enhanced mechanical properties can be also obtained from the energy dissipating effect of rigid HEMA chains in the hydrogels and the interaction between the tertiary amine moieties and hydrophobic effect of gemini methyl groups of PDMAEMA and PHEMA polymer chain pendant moieties. Here, the increase of elastic modulus as HEMA increases may be better understood by taking into account the effective crosslink density of hydrogels ν_e which can be given by Eq (5.8). By using the G_0 and ν_2^0 values together with Eq. (5.8), the effective crosslink density ν_e of copolymer hydrogels was calculated and the results were collected in Figure 6.8 as solid symbols against the comonomer HEMA content. The addition of a small fraction of HEMA led to a significant increase in the effective crosslink density of P(DMAEMA-co-HEMA) hydrogels. For PDMAEMA hydrogels, ν_e is about 3.307 mol / m^3 while it is 85.68 mol / m^3 for copolymer hydrogels containing 90 mol% of HEMA. The dashed curve in Figure 6.8 represents the crosslinking efficiency ε_{xl}, calculated using the equation given by:

$$\varepsilon_{xl} = \frac{\nu_e}{\nu_{chem}} \qquad \textbf{(6.1)}$$

where ν_{chem} is the chemical crosslink density of hydrogels, which would result if all the crosslinker molecules formed effective crosslinks in the resulting hydrogel. Since X = 1/80, ν_{chem} was 193.0 mol/m^3 for PDMAEMA hydrogels. Since the crosslinking agent added during the polymerization reaction is not fully incorporated into the polymer network, ε_{xl} gives the fraction of the crosslinker molecules consumed in the formation of elastically effective crosslinks. The comparison of the parameters ν_e and ν_{chem} showed that the experimentally determined crosslinking density is lower than the theoretical crosslinking density calculated from the initial amount of DEGDMA used for the copolymeric hydrogel synthesis.

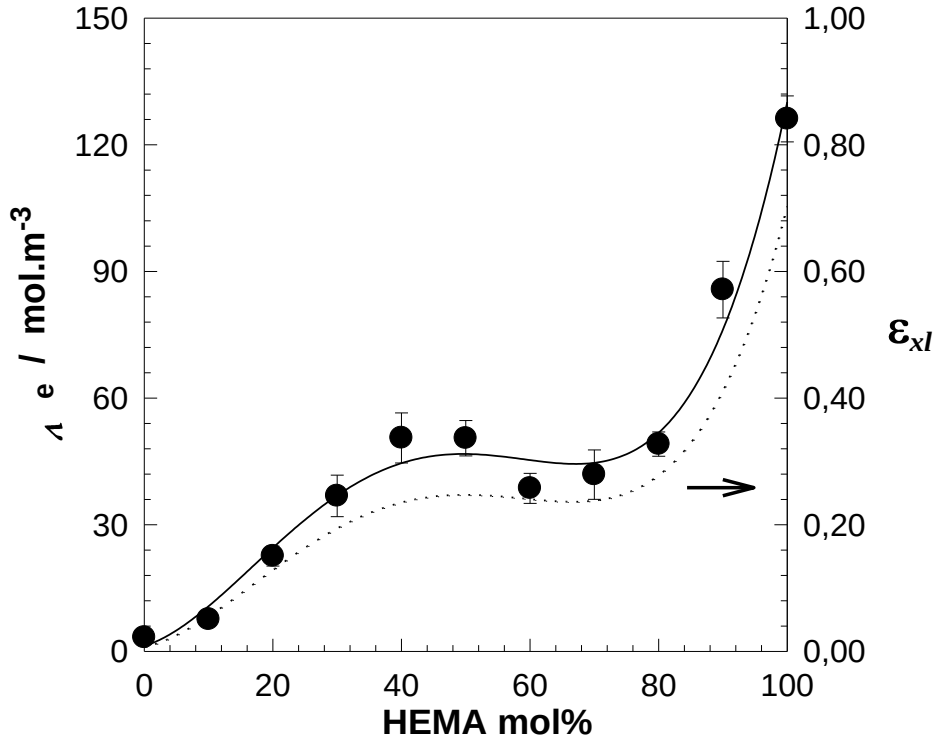

Figure 6.8 : The effective crosslink density ν_e of P(DMAEMA-co-HEMA) hydrogels shown as a function of the comonomer HEMA content by solid symbols. The solid curve shows the trend of the experimental data. The dashed curve represents the crosslinking efficiency ε_{xl} of hydrogels calculated by *Eq. 6.1*.

Hariharan and Peppas studied the effect of the crosslinking ratio on the elasticity of poly(diethylaminoethyl methacrylate-co-hydroxyethyl methacrylate) P(DEAEA-co-HEMA) hydrogels [65]. It was reported that an increase in the crosslinking ratio decreased the modulus due to decreased flexibility of the polymer chains. An increase in pH leads to a decrease in the ionization of the network and reduced

swelling of the network, and hence to an increase in the modulus. Emileh et al. investigated the mechanical properties of PDMAEMA and poly(*N*,*N*-dimethylaminoethyl methacrylate-co-butyl methacrylate) hydrogels and their results showed that the addition of hydrophobic comonomer butyl methacrylate increases the mechanical strength of the network and the apparent crosslinking density is larger than the theoretical value. This result was attributed to the contribution of the additional crosslinks and the presence of entanglements. The hydrophobically aggregated microdomains in the hydrogels, acting as additional crosslinks in the network structure, can contribute to the macroscopically determined crosslinking density of these networks [29].

It can be seen that ν_e increases with the increasing comonomer HEMA content in the feed and this can reasonably explain why P(DMAEMA-co-HEMA) copolymeric hydrogels have excellent mechanical properties. From the comparison of Figures 6.6 and 6.8, it is seen that the dependence of both the elastic moduli G_0 and the effective crosslink density ν_e of P(DMAEMA-co-HEMA) copolymeric hydrogels exhibit three different regimes on the comonomer HEMA content. For HEMA content below 40 mol%, both G_0 and ν_e of hydrogels are increasing functions of HEMA mol%. In this region, an almost ten-fold increase in the elastic modulus was observed. This result obviously shows that the addition of the comonomer HEMA has a strong effect on the elastic properties of PDMAEMA hydrogels. The increase in modulus may be attributed to the cross-linking between polymer chains and swelling. As can be seen from Figure 6.2, the swelling ratio is also high for the copolymeric P(DMAEMA-co-HEMA) hydrogels containing higher DMAEMA content and the swelling of hydrogels decreases with further increasing HEMA mol%. The difunctional crosslinker DEGDMA contains two oxyethylene repeating units, it bears long chain spacer between two vinyl groups and also during the swelling process, the network chains are forced to attain more elongated and less probable configurations. The absorption of water by the hydrogel also causes the network to expand and its chains to stretch. As a result, the chains making up the network structure is assumed in a stretched conformation as the polymer network swells. Since the network chains in these swollen hydrogels are in the expanded configuration with respect to their dry state, the increase of the elastic modulus is connected with high stretching of the network chains.

In the range of HEMA content between 40 and 70 mol%, both G_0 and ν_e decrease slightly with increasing HEMA. In this region, the higher crosslink density may cause stronger thermodynamic force which makes water to diffuse faster. Also, this can be attributed to the fact that the crosslinking agent DEGDMA added during the polymerization reaction was not fully incorporated into the polymer network. For HEMA content above 70 mol%, the effective crosslink density ν_e increases sharply with increasing HEMA content. The rapid increase of ν_e may be interpreted as a result of increasing extent of chain entanglements and the physical cross-link density arising from hydrogen bonding interaction between -OH groups of HEMA and the ether oxygen groups of DEGDMA in this high concentration regime. The elastic moduli of hydrogels also rapidly increase as the HEMA content in the network matrix further increased. As seen from Figure 6.2, in this regime, the swelling of copolymeric hydrogels decreases with increasing HEMA content. As a result, it may be expected that a highly crosslinked network offers a lower rate of swelling. This result may be attributed that a small amount of HEMA can occupy the void space within the polymer network, leading to a more compact gel network. Thus, the swelling degree of P(DMAEMA-co-HEMA) hydrogels is much smaller than that of pure PDMAEMA hydrogels.

Since the crosslink density of hydrogels is related to the swelling ratio, the crosslinker content, the structure of the crosslinker and the copolymer composition, it can be concluded that the PDMAEMA gel strength can be improved by adjusting the crosslink density using appropriate amount of the comonomer HEMA in the preparation. In addition, the structural information is important in analyzing copolymeric hydrogels from microscopic point of view and in further interpreting straightly the enhancement between polymer chains and crosslink points. Physico-mechanical properties of copolymeric P(DMAEMA-co-HEMA) hydrogels determine to a significant degree how suited these hydrogels are for a given application. The elastic modulus data at rubbery region was used to estimate the most important quantifiable characteristic network parameters such as the number-average molecular weight of the polymer chains, M_c, and the number of segments, N, between crosslink points. Obtaining these parameters for P(DMAEMA-co-HEMA) hydrogels indicates to what extent these systems are compatible with the desired degree of swelling. In Figure 6.9(A), N values of P(DMAEMA-co-HEMA) hydrogels is shown as a

function of the mole fraction of HEMA in the monomer mixture. The number of segments between crosslink points is a measure of the physical distance between network chains available for the diffusive movement of water molecules. It was found that increasing the comonomer HEMA in the feed up to 40 mol% rapidly decreases the average network chain length *N* of P(DMAEMA-co-HEMA) hydrogels. As shown in Fig. 6.8, the crosslink density of PDMAEMA hydrogels also inceases in this range. However, further increase in the HEMA content, slightly decreases the *N* values of the hydrogels. The molecular weight between cross-links describes the average macromolecular weight between any two adjacent cross-link points within the three-dimensional structure of the hydrogel matrix. This is essentially a description of the degree of cross-linking of the hydrogel. In Figure 6.9(B), the molecular weight M_c between cross-links of P(DMAEMA-co-HEMA) hydrogels is also shown as a function of the mole fraction of comonomer HEMA. It is seen that an increase in the crosslinking density led to a decrease of the molecular weight between crosslinks in all cases.

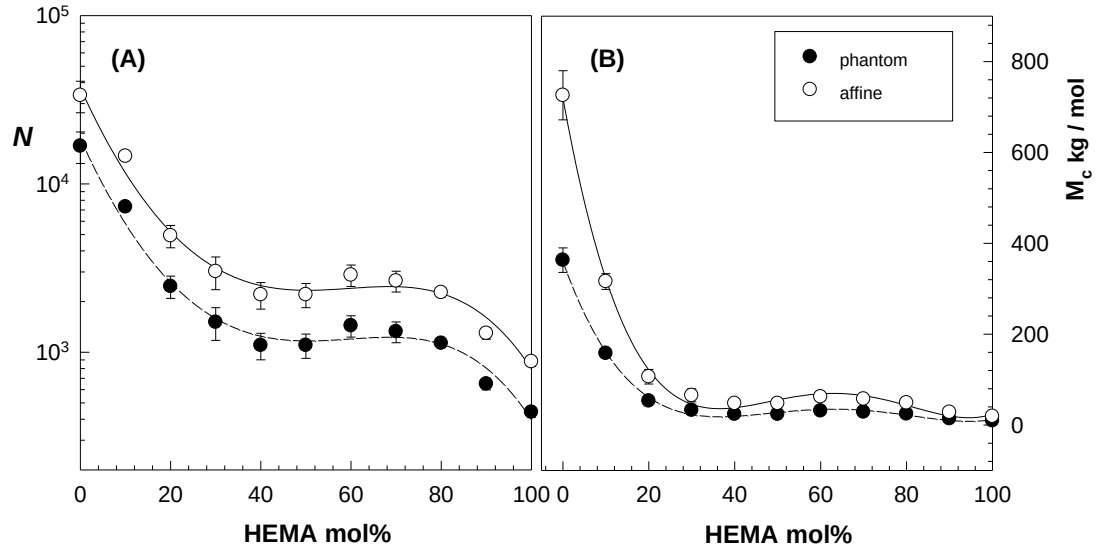

Figure 6.9 : The network chain length *N* (A) and the molecular weight between cross-links M_c of P(DMAEMA-co-HEMA) hydrogels (B) are shown as a function of the mole fraction of HEMA. The filled and open symbols are the calculation results for phantom ($\phi = 4$) and affine network models, respectively.

A denser network structure which leads to higher mechanical strength is responsible for higher crosslinking density and also result in lower average molecular length between cross-links and, therefore, weaken movement of polymer chains. When the gel is stretched, the short-chain network ruptures because of the ineffective

dissipation of energy stored between crack tips. But for the longer chain, the crack propagates through polymer chains movement related to their flexibility. The higher stress at lower crosslinker content demonstrates that the flexibility dominates in the strength of P(DMAEMA-co-HEMA) hydrogels.

6.1.4 Thermodynamics of equilibrium swelling of P(DMAEMA-co-HEMA) hydrogels

The most important contribution to the elucidation of the swelling mechanism of gels was made by Flory and a theoretical investigation was further developed by Rehner [75,76]. Based on this theory, the thermodynamic force of mixing and the elastic force of the polymer chains are the two opposing forces compromising the swelling behavior of a hydrogel. The total Gibbs free energy change during swelling process is given by Eq. (3.14). It is well known that the polymer–solvent interaction parameter is both temperature- and concentration-dependent and the relationship between χ parameter and ν_2 could be fitted well by second degree polynomials as:

$$\chi = \chi_1 + \chi_2 \nu_2 + \chi_3 \nu_2^{\,2} + \cdots \qquad \textbf{(6.2)}$$

where the coefficients χ_1, χ_2, χ_3,… are functions of temperature and the molecular characteristics of the polymer–solvent system. Assuming isotropic swelling, the elastic contribution, ΔG_{el}, can be evaluated from the elastic free-energy change during swelling given by:

$$\Delta G_{el} = \frac{3}{2}\left(\frac{RT}{NV_1}\right)(\alpha^2 - 1 - \ln \alpha) \qquad \textbf{(6.3)}$$

where α is the linear deformation ratio relative to the after-preparation state of gel and related to the equilibrium swelling as $\alpha = D/D_0 = \mathrm{V}_{\mathrm{eq}}^{1/3}$. The equilibrium swelling data collected in Figs. 6.2 and 6.3 showed that P(DMAEMA-co-HEMA) hydrogels containing higher amount of DMAEMA are highly swollen in water, for such highly swollen hydrogels, the swelling equilibrium is mainly determined by the mixing entropy which is balanced by the gel rubberlike elasticity. According to the

theory of rubber elasticity, the free energy of elastic deformation ΔG_{el} scales with the deformation ratio as [75,77]:

$$\Delta G_{el} \approx N^{-1} \alpha^2 \tag{6.4}$$

On the other hand, as predicted by the Flory-Rehner theory, for highly swollen hydrogels in a good solvent, the linear swelling ratio α scales with the network chain length N as $\alpha \approx (\nu_2^0 N)^{1/5}$. Then, the volume of the equilibrium swollen gels may be written as:

$$V_{eq} \approx (N\nu_2^{0})^{3/5} \tag{6.5}$$

which indicates a scaling parameter of 0.6 between the equilibrium swollen volume V_{eq} of hydrogels and the gel preparation concentration per network chain. In Figure 6.10, the volume of the equilibrium swollen P(DMAEMA-co-HEMA) hydrogels is plotted as a function of the product $N\nu_2^0$ on double-logarithmic coordinates.

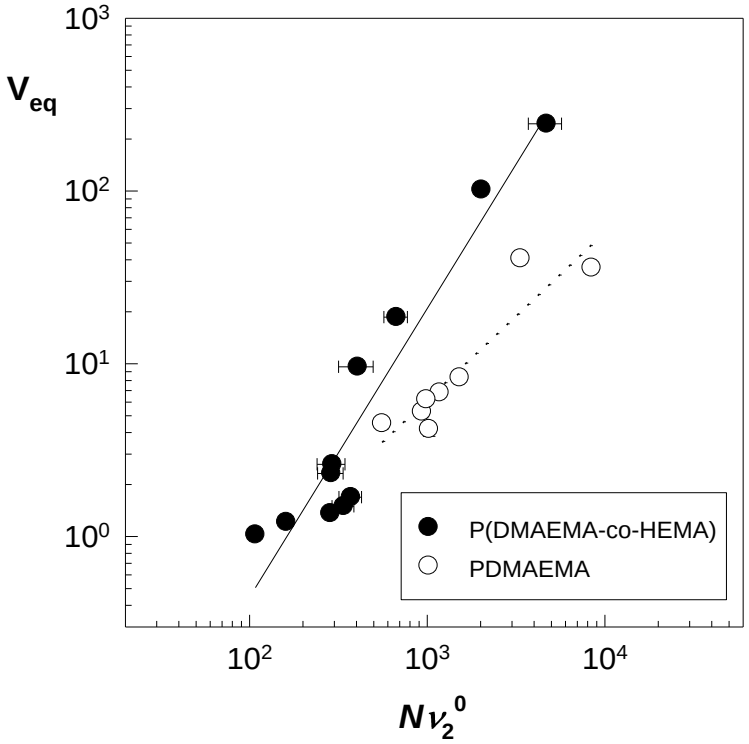

Figure 6.10 : The equilibrium volume swelling ratio of P(DMAEMA-co-HEMA copolymeric hydrogels *Veq* (filled symbols) and of PDMAEMA hydrogels (open symbols) shown as a function of $N\nu_2^0$. The data for PDMAEMA hydrogels were taken from the literature [108].

Experimental data are shown by filled symbols for P(DMAEMA-co-HEMA) copolymeric hydrogels. For comparison, the swelling data reported for PDMAEMA hydrogels of crosslinker ratio X = 1 / 80 is also shown in the figure by open symbols [108]. The curves in the figure are the best fitting curves to the experimental data of hydrogels. It can be seen that while the gel preparation concentration varies greatly, all the data of resulting P(DMAEMA-co-HEMA) hydrogels falls onto a single curve with a scaling parameter 1.61 $\pm$ 0.02 while it was 0.96 $\pm$ 0.01 for PDMAEMA hydrogels. The scaling parameter for P(DMAEMA-co-HEMA) hydrogels, thus found, is larger than the predicted value of the theory which indicates that the higher swelling capacity of P(DMAEMA-co-HEMA) hydrogels becomes more significant at higher gel preparation concentrations. This result also indicates the importance of the gel preparation concentration in the treatment of the swelling behavior and the elasticity of the resulting hydrogels.

From Eqs. (5.7), and (5.8), the reduced modulus G_r defined as the ratio of the elastic modulus of the equilibrium-swollen gel to that of the same gel after its preparation is calculated by:

$$G_r = \frac{G}{G_0} = \left(\frac{\nu_2}{\nu_2^0} \right)^{1/3} = V_{eq}^{-\frac{1}{3}} \qquad \textbf{(6.6)}$$

and the results were plotted against the equilibrium gel volume V_{eq} in Figure 6.11. According to the theory used for the thermodynamics of gel swelling, the reduced modulus G_r of gels should decrease continuously with the swelling due to the decrease of the concentration of the elastically effective network chains. According to Eq. (6.6), the double-logaritmic G_r versus V_{eq} plot should exhibit a slope of -1/3 for Gaussian chains. The solid curve is the best fit to the experimental data, which gives an exponent -0.16 $\pm$ 0.03 but the variation is larger than the theoretical expectation and when the higher terms for V_{eq} are ignored, the scaling parameter becomes -0.36 $\pm$ 0.04, which is close to the theoretical value of -1/3. Hence, it was observed that the reduced modulus of P(DMAEMA-co-HEMA) hydrogels decreases as the gel swells beyond its swelling degree after preparation and deviation from the theory occurs at higher swelling ratio. The results showed good relation with the theory at a lower swelling ratio.

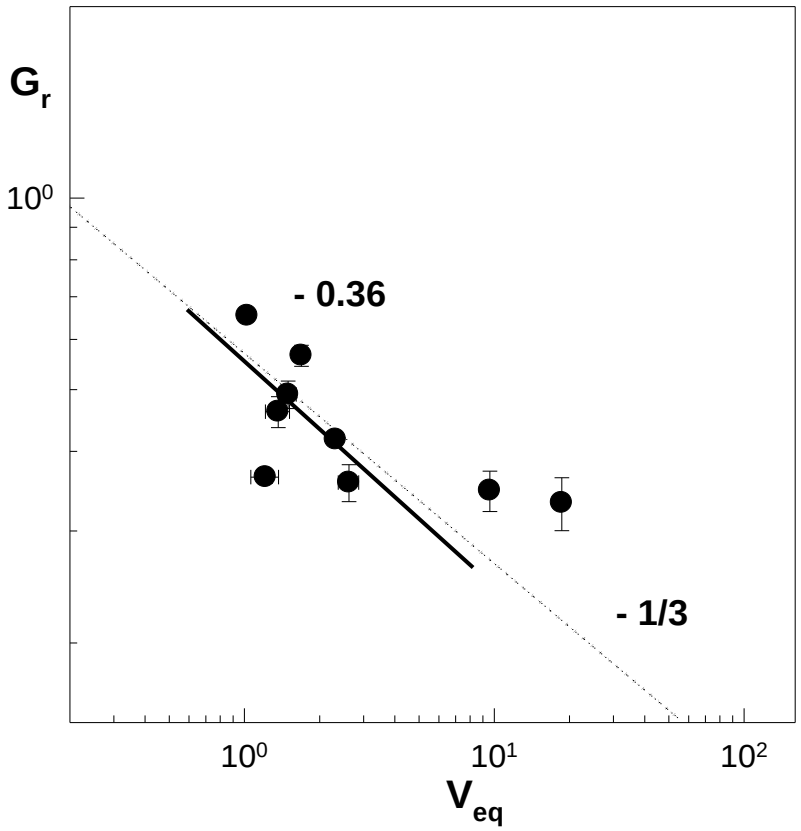

Figure 6.11 : Reduced modulus G_r shown as a function of the volume of equilibrium swollen gel V_{eq}. The solid curve is the best fit to the experimental data. The dotted curve represents the prediction of Eq. (6.6). The corresponding slopes are already shown.

6.1.5 Interaction parameter of P(DMAEMA-co-HEMA) copolymer network–water system

Since the swelling of gels is strongly affected by the polymer–solvent interaction parameter, χ, the swelling behavior of P(DMAEMA-co-HEMA) copolymeric hydrogels was also analyzed by using Flory-Rehner theory of swelling equilibrium [76]. Upon differentiation of the total free energy of swelling $\Delta G_{swelling}$ with respect to the water molecules in the system, the following expression can be derived for the interaction parameter χ between the P(DMAEMA-co-HEMA) network and water:

$$\chi = -\frac{\ln\left(1-\nu_2\right)+\nu_2+0.5\left(\rho/\overline{M}_c\right)V_1\left(\nu_2\right)^{1/3}\left(\nu_2^0\right)^{2/3}}{\left(\nu_2\right)^2} \qquad \textbf{(6.7)}$$

The temperature sensitive swelling behavior of P(DMAEMA-co-HEMA) copolymer hydrogels was also analyzed within the framework of the Flory–Rehner theory of

swelling equilibrium. By using the experimentally determined equilibrium swelling ratios and the M_c values of gels, the interaction parameters χ of the P(DMAEMA-co-HEMA) – water system were calculated at different temperature and polymer volume fraction ν_2. The results of the calculations were collected in Figure 6.12 (A) and (B) plotted as functions of the polymer concentration ν_2 and the inverse temperature 1/T, respectively. Least squares analysis of the data points χ and ν_2 of P(DMAEMA-co-HEMA) copolymer hydrogels gave the following relationship for the dependence of χ on ν_2:

$$\chi = 0.422 + 1.639\nu_2 - 6.620\nu_2^{\,2} + 11.531\nu_2^{\,3} \qquad \textbf{(6.8)}$$

The interaction parameters χ of the P(DMAEMA-co-HEMA) – water system calculated at 25°C were given in Table 6.1. It was found that the interaction parameter χ of the P(DMAEMA-co-HEMA) – water system increase with increasing HEMA content which is expected due to increase in the interactions between hydrophobic groups of the polymer chains.

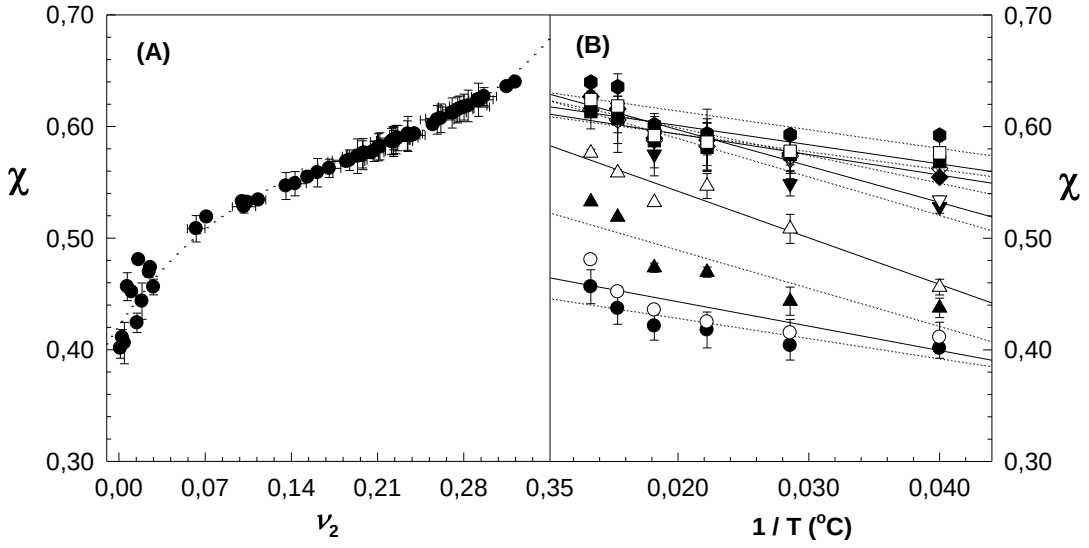

Figure 6.12 : The polymer–solvent interaction parameter χ for the P(DMAEMA-co-HEMA) copolymer network–water system shown as functions of the polymer concentration ν_2 (A) and the inverse temperature 1/T (B). HEMA mol%: 0 (●), 10 (○), 20 (▲), 30 (△), 40 (▼), 50 (▽), 60 (◆), 70 (◇), 80 (■), 90 (□) and 100 (⬢).

Bahar et al. prepared PHEMA by cross-linking with various amounts of ethylene glycol dimethacrylate and the degree of swelling of the networks in diethylene glycol was measured in the range $0 < \nu_2 < 0.35$ as a function of cross-link density. An expression of the form $\chi = 0.49 - 0.25\nu_2$, was estimated at 25 ^{o}C [109]. The values of polymer–solvent interaction parameter at different temperatures for P(DMAEMA-co-HEMA) hydrogels with different contents of HEMA were also collected in Table 6.2.

Table 6.1 : Polymer-solvent interaction parameter χ at 25^{o}C and the enthalpy and entropy changes appearing in the χ parameter for the P(DMAEMA-co-HEMA) copolymer–water systems at different values of HEMA content.

HEMA mol%	χ	ΔS (J/mol K)	ΔH (J/mol)
0	0.401 (0.0895)	-3.861	-15.000
10	0.411 (0.0353)	-4.046	-18.135
20	0.438 (0.0087)	-4.636	-28.382
30	0.456 (0.0071)	-5.200	-34.656
40	0.528 (0.0057)	-5.474	-28.623
50	0.534 (0.0035)	-5.506	-27.052
60	0.555 (0.0001)	-5.393	-20.625
70	0.563 (0.0082)	-5.384	-13.895
80	0.569 (0.0135)	-5.199	-13.199
90	0.576 (0.0180)	-5.281	-14.263
100	0.592 (0.0019)	-5.384	-13.895

Table 6.2 : Polymer-solvent interaction parameter χ at different values of HEMA content and temperatures.

T(^{o}C)	0 mol% HEMA	20 mol% HEMA	40 mol% HEMA	60 mol% HEMA	80 mol% HEMA	100 mol% HEMA
25	0.401	0.438	0.528	0.555	0.569	0.592
35	0.404	0.444	0.549	0.576	0.575	0.593
45	0.418	0.470	0.588	0.588	0.581	0.593
55	0.421	0.474	0.575	0.590	0.587	0.602
65	0.437	0.519	0.612	0.616	0.607	0.636
75	0.457	0.533	0.624	0.627	0.613	0.640

As can be seen that an increase in the temperature increases the interaction parameter which is consistent with the fact that all P(DMAEMA-co-HEMA) hydrogels have a

lower critical solution temperature (LCST) in water. Another point shown from the data is that increasing the amount of comonomer HEMA leads to an increase in the χ parameter due to the incorporation of HEMA into the network structure also lead to a reduction in the solubility of the polymer in water. The total interaction parameter χ is composed of enthalpic and entropic contributions [75]. For large swelling ratios, the dependence of χ on ν_2 can be neglected and χ reduces to χ_1 by the following equation:

$$\chi_1 = \frac{\Delta G}{RT} = \frac{\Delta H - T\Delta S}{RT} \qquad \textbf{(6.9)}$$

The changes in the enthalpy ΔH, and entropy ΔS values appearing in the χ_1 parameter of P(DMAEMA-co-HEMA) copolymer network–water system were calculated from the slope and the intercept at 1/T = 0 of the linear regression lines in Figure 6.12 (B).

The calculation results of ΔH and ΔS were also collected in Table 6.1. It was observed that both quantities are negative for all the copolymeric hydrogels. Since polymer–solvent systems possessing the LCST are characterized by negative values of both ΔH and ΔS, the results indicated that all the P(DMAEMA-co-HEMA) copolymeric hydrogels have LCST's. The absolute values of both ΔH and ΔS increase with increasing HEMA indicating that the temperature sensitivity of the hydrogels also increases with increasing amount of HEMA and this meant that the fraction of structured water increased with decreasing total water content at elevated temperatures. The decrease in entropy could be attributed to the structuring of water, which is more manifested upon the solvation of hydrophobic groups and the decrease in enthalpy could be attributed to the increase in water structuring and enhancing in hydrogen bonding.

6.2 pH-response of P(DMAEMA-co-HEMA) Copolymeric Hydrogels

To investigate the influence of pH on the equilibrium swelling degree of P(DMAEMA-co-HEMA) hydrogels, the swelling measurements were first measured in solutions at various pH levels from 2.1 to 11.2 at room temperature. Figure 6.13 shows the changes in the equilibrium swelling of P(DMAEMA-co-HEMA)

hydrogels containing various ratios of HEMA with changing pH values as a three-dimensional plot. Based on the feature of DMAEMA, P(DMAEMA-co-HEMA) hydrogels exhibited pH-responsive behavior. It was observed that the swelling ratio of P(DMAEMA-co-HEMA) copolymeric hydrogels is significantly affected as the pH of the swelling media and the composition of the copolymer network changes. In contrast to PHEMA, the copolymers with DMAEMA exhibited a dramatic change in the equilibrium swelling degree between the collapse and the expanded state. In the molecular structure of DMAEMA, there is an active quarternizable tertiary amino group [-$N(CH_3)_2$)] which contributes charge and pH sensitivity to the network and the protonation of the tertiary group could induce the swelling ratio to change with changing pH in aqueous solutions. The swelling capacity of hydrogels increases as the acidity of the swelling medium increases. In all compositions, the maximum extent of swelling were obtained at the lowest pH of 2.1, this being due to complete protonization of amino groups of DMAEMA at this pH value. The protonation degree of tertiary amino group increases the charge density of the network and causing the P(DMAEMA-co-HEMA) hydrogels to swell. The tertiary amino groups are charged in the range of pH 2.1–7.7, which leads to the generation of electrostatic repulsion between polymer chains, hence, P(DMAEMA-co-HEMA) hydrogels remain in the swollen state in acidic pH region.

It was observed that the degree of swelling of P(DMAEMA-co-HEMA) hydrogels decreases with increasing pH. Because positively charged tertiary amino groups are incorporated into the polymer network, the gel swells in the low pH region, due to the ionic repulsion of the protonated amino groups, and collapses in the high pH region, due to unprotonated amino groups. Since the protonation of amino groups of hydrogel matrix is easier in acidic medium than basic medium, an increase in the pH from 7.7 to 8.0 decreased the water uptake and the equilibrium swelling degree of hydrogels dramatically and hence, P(DMAEMA-co-HEMA) hydrogels showed pH-dependent volume transition behavior. This is due to the fact that as the alkalinity of the buffer solution increases, the concentration of ionized groups in the polymer decreased drastically. Hence the resultant electrostatic repulsion decreases, thereby reducing the swelling and the water uptake. The increase in the mobile counterion content of the network increases the internal osmotic pressure which in turn induces the observed pH-dependent transition in the range of pH between 7.7 and 8.0.

Another point shown from Figure 6.13 is that P(DMAEMA-co-HEMA) hydrogels were in the collapsed state in regions more alkaline than pH 8.0. This phenomenon is due to two factors firstly no more extra tertiary amino group is ionized in this case and secondly, the more compact hydrogel network due to the hydrogen bond formed among the tertiary amino group and the hydrophobic aggregation. While pH changes from 8.0 to 11.2, the hydrophilicity of P(DMAEMA-co-HEMA) chains decreases gradually with the increase of pH value, leading to the decrease of binding interaction between water and polymer matrix. The electrostatic repulsion between PDMAEMA segments also decreases while the amount of amino groups from PDMAEMA decreased drastically. Thus, the mesh size becomes smaller and the capacity of hydrogels for water uptake decreases.

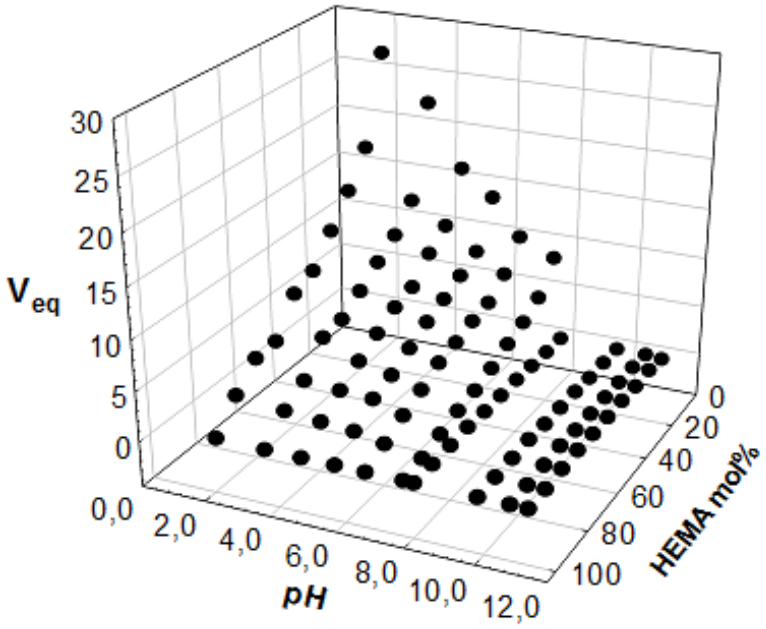

Figure 6.13 : The effect of pH on the equilibrium swelling behavior of P(DMAEMA-co-HEMA) hydrogels with different HEMA concentrations. The swelling measurements were carried at room temperature.

6.2.1 Effect of temperature on pH-dependent swelling of P(DMAEMA-co-HEMA) copolymeric hydrogels

In order to analyze dual pH- and temperature- sensitivity of P(DMAEMA-co-HEMA) copolymeric hydrogels, the swelling studies were also carried out at various temperatures for the whole range of composition. The effect of temperature on the equilibrium swelling ratio of produced hydrogels was given as a function of pH in

Figure 6.14. The results indicated that the equilibrium swelling ratio of the hydrogels is strongly dependent on both pH and temperature.

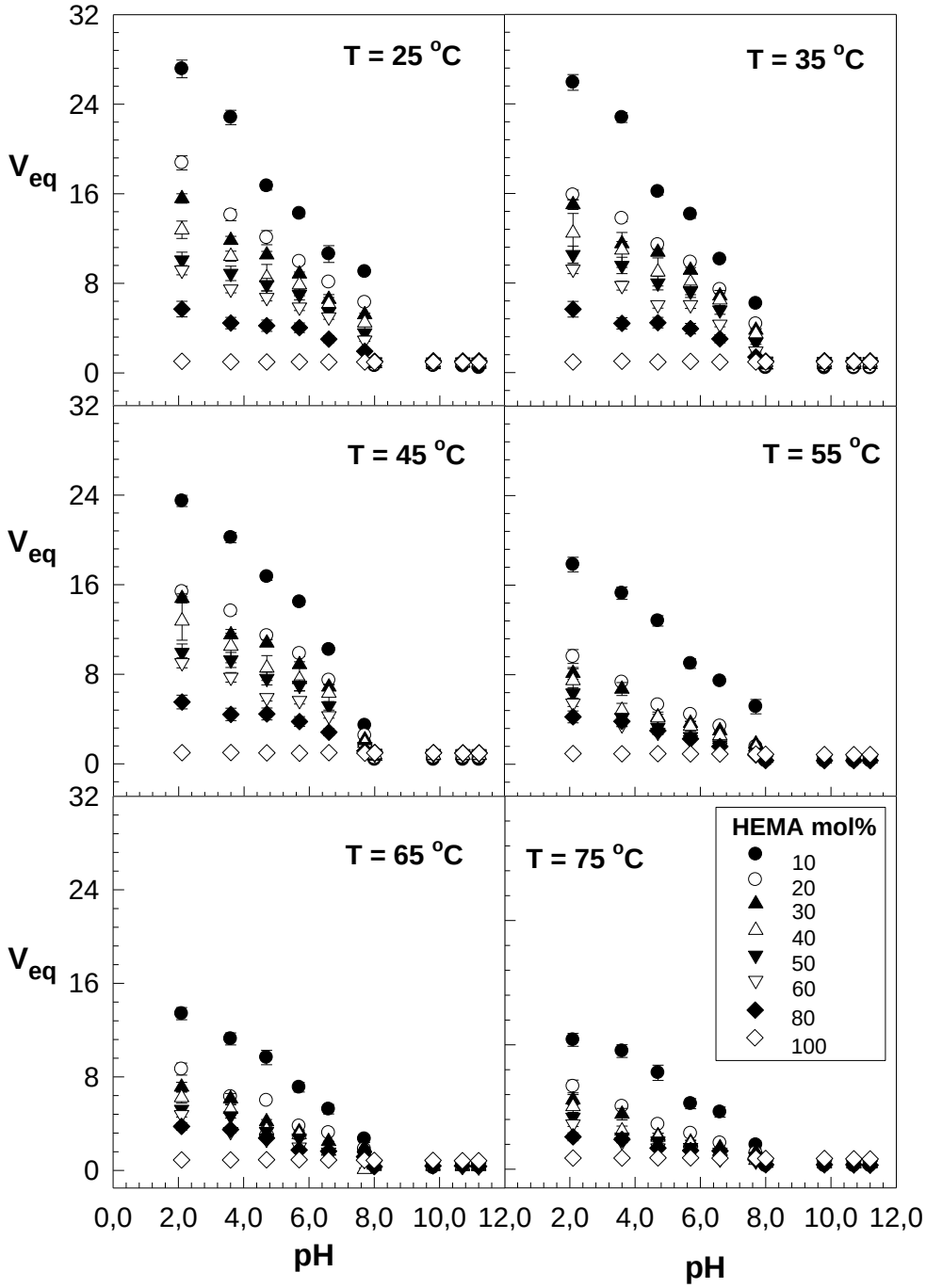

Figure 6.14 : The equilibrium swelling ratio of P(DMAEMA-co-HEMA) hydrogels as a function of pH at different temperatures. The temperature and HEMA contents of the hydrogels (HEMA mol%) are already indicated in the figure.

It can be seen that the equilibrium swelling ratio of P(DMAEMA-co-HEMA) hydrogels increases at low pH and at greater DMAEMA content since the hydrogel

becomes positively charged in solutions of low pH. In the range of temperature between 25 and 45 ^{o}C, the temperatures below the LCST of the copolymers, the temperature-dependent behavior is quite similar. At a particular temperature, as the pH is lowered to the acidic region, the equilibrium swelling ratios of P(DMAEMA-co-HEMA) hydrogels are much higher than that of in basic solutions, which might be mainly contributed to hydrogen bond and electrostatic interaction. In acidic pH region, $-N(CH_3)_2$ groups of the network chains can be integrated with H^+ ions into $-NH^+(CH_3)_2$ groups and electrostatic repulsion causes the network to expand, resulting in greater water uptake and producing a larger swelling ratio. When the pH of the swelling medium is increased, the amount of $-NH^+(CH_3)_2$ is gradually reduced inside the hydrogels, which leads to a decrease in osmotic pressure and makes the swelling ratio of the hydrogels smaller. When the temperature is below 45^{o}C, the hydrogels are in the swollen state due to the binding water caused by the hydrogen-bonding force between the water and the polymer chains. Since the hydrogen-bonding force is reduced by increasing the temperature, the binding water turns to the free water which can be moved out of the polymeric network structure. This fact becomes more evident with increasing temperature. In fact, at temperatures above 45 ^{o}C, the extent of the pH-induced collapse transition decreases for the whole range of composition. In this range of the temperature, the free water will be moved from the hydrogel matrix into the solution and the equilibrium swelling ratio of P(DMAEMA-co-HEMA) hydrogels will be further decreased since the attraction force of the water and polymeric chain is lower that the dispersion force of the water molecules.

For the hydrogels of DMAEMA copolymerized with hydrophobic comonomers, Siegel and Firestone [25] found a systematic reduction in pH at which the swelling transition occurs as the hydrophobic comonomer increased. Their results showed that the transition will occur when a particular balance of osmotic and hydrophobic forces is achieved. A greater degree of ionization is required to enable the transition as network hydrophobicity increases. They also reported the relatively sharper volume transitions at pH 7.0 for alkylmethacrylate-DMAEMA copolymer gels. Other authors have reported that the pH-sensitive or temperature-sensitive phase transition behavior of poly(2-dimethylaminoethyl methacrylate-co-butyl methacrylate) can be changed by the temperature or pH of the swelling medium at constant hydrogel composition [29]. The incorporation of butyl methacrylate into the gel structure

reduces the pH and temperature-sensitive phase transition points, respectively. A plausible explanation for this behavior was given by Plamper et al. [110] who reported a change in the slope of the pH–temperature curve at LCST and also found that the cloud points of PDMAEMA in buffer solutions can be easily tuned by changing the pH, molecular weight, and concentration. The results were attributed to a hindering of the amino groups ionization due to an increase in the local density (intra- and intermolecular aggregation). Their results also indicated that phase separation in PDMAEMA solutions induced by an increase in temperature can be satisfactory described by the classical Flory-Rehner theory in terms of the interaction parameter χ which designates the change in the interaction energy when the polymer and solvent are mixed together [76].

6.2.2 Effect of composition on pH-dependent swelling of P(DMAEMA-co-HEMA) copolymeric hydrogels

The effect of comonomer HEMA on the water content of copolymeric P(DMAEMA-co-HEMA) hydrogels was studied by monitoring the change of volume swelling as a function of the temperature. Figure 6.15 shows the relation of pH and swelling ratio of P(DMAEMA-co-HEMA) copolymeric hydrogels. The composition of the copolymers was varied widely between cationic homo-monomer (DMAEMA) and anionic homo-monomer (HEMA). The data in Figure 6.15 clearly showed that, the swelling of P(DMAEMA-co-HEMA) hydrogels strongly depend on the concentration of comonomer HEMA in the feed. Increase in HEMA content in the network reduced swelling degree dramatically at all pH values, especially, when the concentration of HEMA was relatively high. Higher equilibrium swelling ratios were obtained by increasing the DMAEMA content of the hydrogel structure. An increase in the DMAEMA/HEMA ratio increases the concentration of ionizable groups and therefore increases the extent of swelling of these copolymer hydrogels. In other words, an increase in HEMA content decreases the concentration of ionizable amino groups, thereby lowering the osmotic pressure that can be generated by the counterions. Thus, the hydrogels swelled in acidic condition and shrank in alkaline condition, when the copolymer was DMAEMA rich composition. It was also observed that as the amount of the tertiary amine, DMAEMA, incorporated into the hydrogel was increased up to 100 mol %, there was a 30-35% increase in hydration as the pH was lowered from 8.0 to 2.1. This degree of hydration was, however,

reduced upon the introduction of increasing concentrations of HEMA into the copolymeric gels since the binding water is kept outside of the hydrogels and insignificantly affected by the change of the temperature. The dependence of water uptake of P(DMAEMA-co-HEMA) hydrogels on pH value is attributed to the presence of tertiary amino groups in PDMAEMA network backbone. Since pKa of PDMAEMA is 7.0–7.3, in an acidic medium, the free amino groups in the networks are ionized, which generates the electrostatic repulsion and breaks hydrogen bonding among polymer chains. Therefore, a higher swelling ratio could be obtained for the copolymeric hydrogels. Reversely, in an alkaline medium, PDMAEMA is deionized and become less hydrophilic. At the same time, hydrogen bonding would exist intensely in P(DMAEMA-co-HEMA) copolymeric network and restrict the movement or relaxation of network chains. As a result, the hydrogel network becomes compact and swelling ratio is lowered.

Another point shown from the Fig. 6.15 is that the pH-dependent volume transition of P(DMAEMA-co-HEMA) copolymer hydrogels disappears with increasing the HEMA content of the copolymer structure. pH-dependent phase transition in the hydrogels containing 60 mol% HEMA was not as sharp as those obtained with 10 mol% HEMA and completely disappears for 100 mol% HEMA. Increasing the HEMA content in the copolymer structure decreased the swelling capacity of the hydrogels and the extent of the pH-sensitive volume transition. The effect of increasing temperature or HEMA content can be explained by the role of hydrophobicity in the volume transition behavior of hydrogels. At a constant pH, incorporation of the hydrophilic comonomer increases the gel hydrophilicity which in turn lowers the amount of amino side groups of DMAEMA chains in the network structure and the degree of protonation which also causes a gradual decrease in the swelling ratio of the hydrogels. The (CH_3) N(CH_3) group of DMAEMA is believed to be more hydrophobic than HEMA which has -OH groups, imparting a hydrophilic nature to the hydrogel system. This decrease results probably from the increasing interaction between the pendant groups of networks in comparison to that between pendant groups and water. The presence of a temperature nonresponsive comonomer HEMA in the copolymer gel structure possibly provided a continuous decrease in the linear swelling ratio.

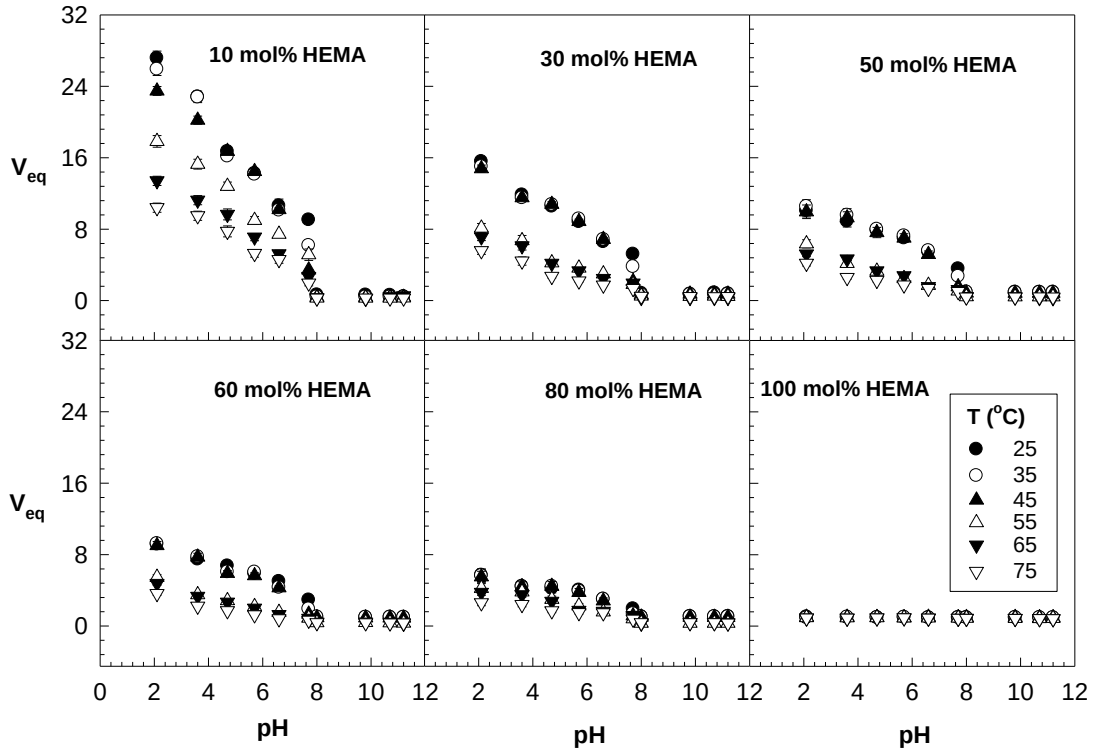

Figure 6.15 : The variation of the equilibrium swelling ratio of P(DMAEMA-co-HEMA) hydrogels as a function of pH at different temperatures. HEMA contents of the hydrogels (HEMA mol%) are already indicated in the figure. T (^{o}C): 25 (●), 35 (○), 45 (▲), 55 (△), 65 (▼), 75 (▽).

It can be concluded that the concentration of DMAEMA, temperature, pH and the copolymer composition are the important factors affected on the characteristic features of the swelling and the volume transition behavior of P(DMAEMA-co-HEMA) copolymeric hydrogels. The pH responsiveness of the copolymers depends on the hydrophobic balance and the extent of the pH-dependent volume transition of the copolymers can be modulated by changing the composition and temperature. This dual responsiveness together with the large extent of the transition from the hydrophilic state to the collapsed hydrophobic state, makes this system promising for biomedical applications.

Since DMAEMA has an aliphatic tertiary amino-groups, pH value of the swelling medium also affect its thermo-responsive swelling behavior. In Figure 6.16, the equilibrium swelling of P(DMAEMA-co-HEMA) hydrogels as function of both the composition and the temperature are shown as three-dimensional plots for pH 2.1, 5.7, 7.7 and 8.0 solutions (Fig. 6.16A-D), respectively. Figure 6.16 provides evidence that the equilibrium swelling is mainly governed by the protonation of

tertiary amino-groups in the polymer. As pointed out previously, at low pH values, the amino groups are positively charged, so that the hydrogels behave as polyelecrolytes and absorbe large amounts of water. This is due to the increasing positive ionic nature of amine groups and increasing repelling effect. The amino groups become unprotonated at higher pH values leading to the decrease in the swelling ratio.

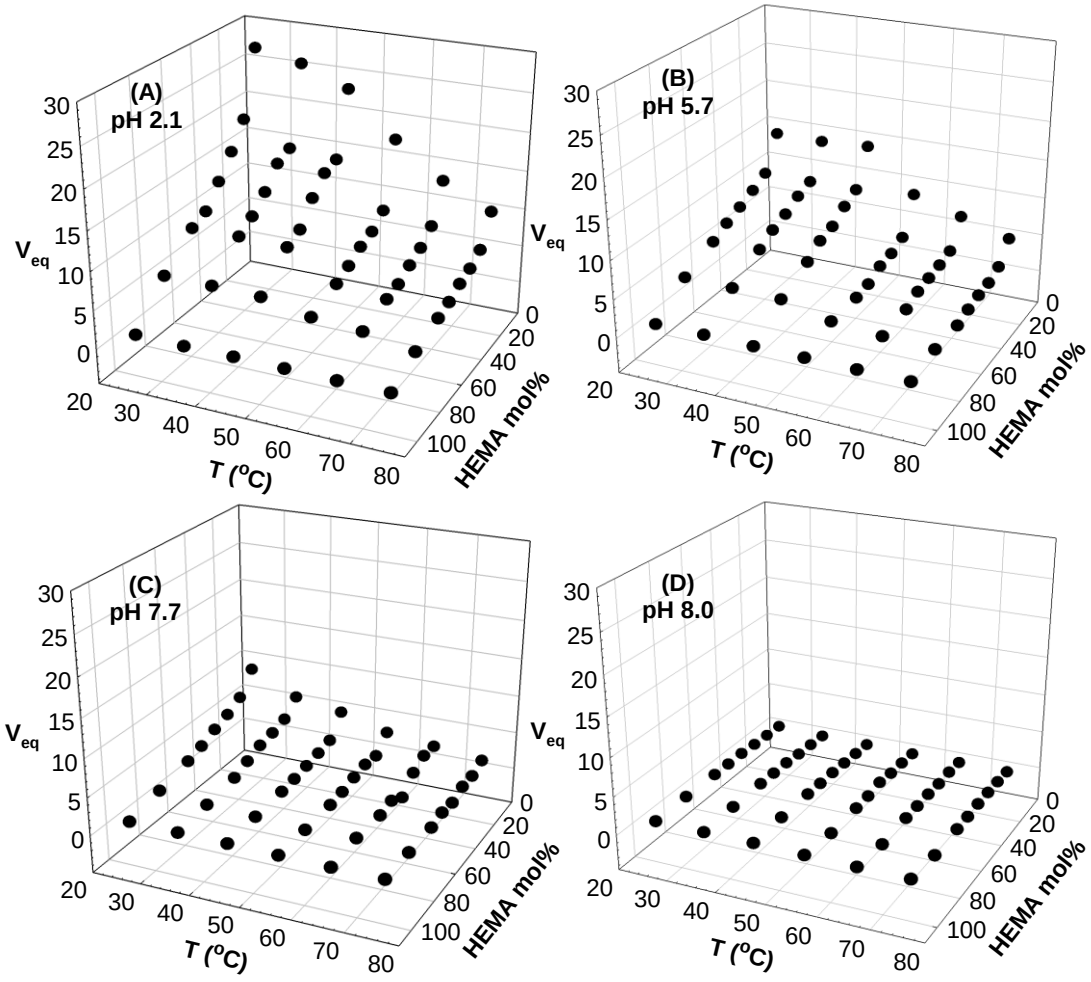

Figure 6.16 : Three-dimensional plots presenting the equilibrium swelling of P(DMAEMA-co-HEMA) hydrogels as a function of HEMA composition and temperature at (A) pH 2.1, (B) pH 5.7, (C) pH 7.7 and (D) pH 8.0.

When the pH was lower than 7.7, the copolymeric hydrogels are in swollen state and the swelling ratio of hydrogels increases up to 20-30 times of their initial volume, but shows minimum at pH 8.0. pH-dependent swelling ratio change of P(DMAEMA-co-HEMA) hydrogels indicated a discontinuous change in the range of pH between 7.7 and 8.0, which is similar to the results reported by Siegel et al. [25]. At pH 8.0, above

the pKa, the amino groups are uncharged resulting in an increase of the hydrophobic interactions for the whole range of compositions that causes lower values of the equilibrium swelling of P(DMAEMA-co-HEMA) hydrogels than those obtained at acidic pH and the hydrogels remain in the collapsed state within the temperature range from 25 to 75 °C. The changing pH value should influence the degree of protonation of tertiary amino group of DMAEMA, which would change the polymer hydrophilicity. The highly protonated tertiary amino group in acidic medium will increase the polymer hydrophilicity, thus resulting in the increase of swelling ratio. The analysis of the composition and temperature dependence behavior at pH 2.1, 5.7 and 7.7 in Fig. 6.16A,B and C showed a nice modulation of the pH- and temperature-dependent transition as a function of the composition. With increasing DMAEMA content in the copolymer, the collapsing temperature moves around 45 ^{o}C, at the same time, hydrogels in the swollen state present high swelling ratio. Therefore, P(DMAEMA-co-HEMA) hydrogels could be attractive for bioengineering applications since the volume transition occurs with a considerable change in the hydrogel volume at physiological pH and, on the other hand, the temperature can be modulated by changing the copolymer composition. This drastic change in the hydrogel volume can also be seen in the photographs shown in Fig. 6.17 taken from P(DMAEMA-co-HEMA) hydrogel sample containing 20 mol% HEMA after equilibrium swelling in pH 7.7 (left) and 8.0 (right) by a digital camera (Sony, Cyber-shot, 8.1 Mega pixel).

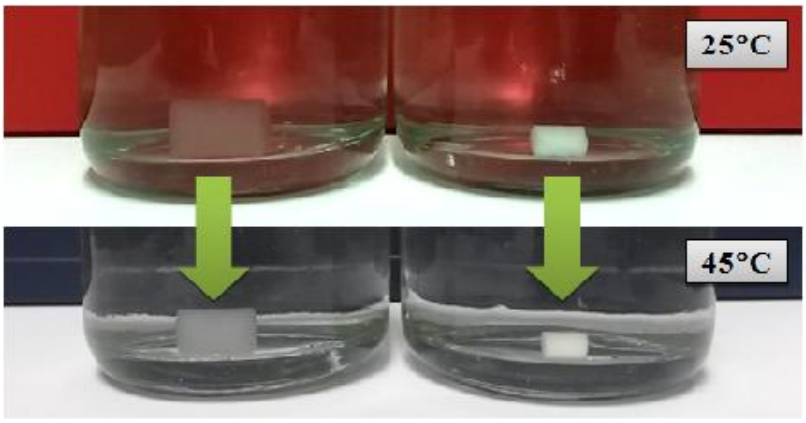

Figure 6.17 : Photographs of P(DMAEMA-co-HEMA) copolymeric hydrogel sample containing 20 mol% HEMA after equilibrium swelling in pH 7.7 (left) and 8.0 (right) at T = 25°C (upper panel) and at 45°C (lower panel).

6.2.3 Polymer–solvent interaction parameter of P(DMAEMA-co-HEMA) copolymer network–water system in pH solutions

For P(DMAEMA-co-HEMA) hydrogels with different contents of HEMA, the polymer–solvent interaction parameter χ at pH 2.1 and 25 ^{o}C was also calculated using the Flory-Rehner equation and the results were collected in Table 6.3. It was found that the χ parameter of P(DMAEMA-co-HEMA) - water system slightly increases with increasing HEMA content in the comonomer feed which is consistent with the fact that these materials have a lower critical solution temperature (LCST) in water. Although HEMA is a hydrophilic monomer, its incorporation in hydrogel chemical structure leads to a reduction in the solubility of the polymer in water. χ parameter of P(DMAEMA-co-HEMA) hydrogel containing 10 mol% HEMA was found as 0.475, however, for the homopolymer hydrogel containing 100 mol% HEMA, it was determined as 0.593. The lower values of χ mean a strong interaction between the polymer network-water and a weak interaction between hydrophobic groups of the polymer chains. This may be explained by the fact that the copolymeric hydrogels swelled to a very high degree in the buffer solution of pH 2.1. Therefore, the temperature, pH and the hydrogel chemical composition all significantly affect the value of the interaction parameter.

6.2.4 Elasticity of P(DMAEMA-co-HEMA) hydrogels under different pH conditions

Though PDMAEMA hydrogels show pH- and thermo-responsive behavior, the lack of the mechanical strength would limit their application. In order to solve this problem and also to vary the swelling ratio, the copolymers of DMAEMA were prepared in the presence of the comonomer HEMA and the mechanical properties including the compression modulus of the hydrogels were tested. After equilibrium swelling in buffer solutions, each sample was subjected to uniaxial compression and the stress-strain data was collected in Figure 6.18. The resulting P(DMAEMA-co-HEMA) copolymeric hydrogels showed substantially improved mechanical properties compared to those of the PDMAEMA hydrogels. According to the theory of rubber elasticity and the stress–deformation function, the slope of the stress - strain curves at small strains is equal to the Young's modulus G of hydrogels. The slope of these lines was used to calculate G of P(DMAEMA-co-HEMA) hydrogels.

In Figure 6.19, the elastic modulus of copolymeric hydrogels after equilibrium swelling in buffer solutions was shown as a function of pH at 25 ^{o}C.

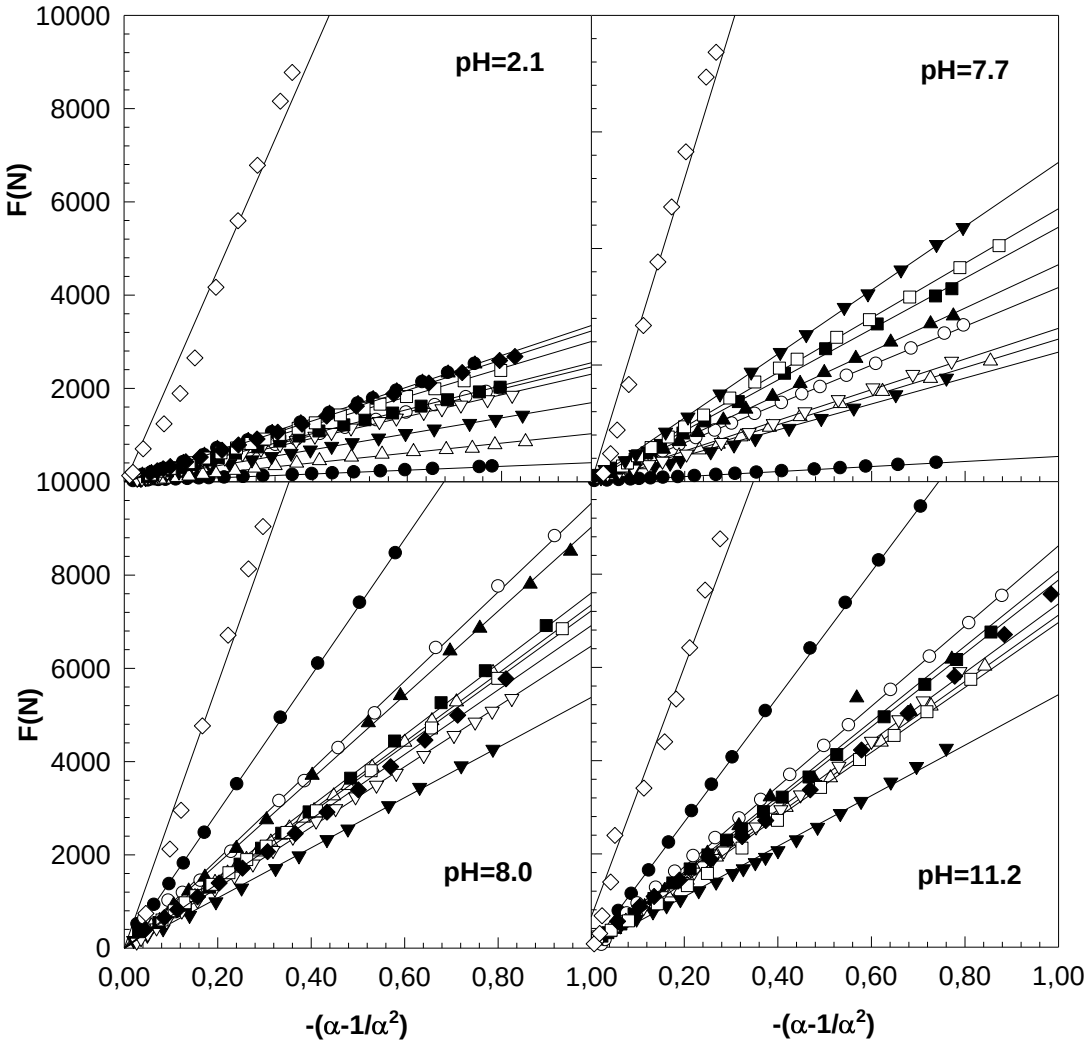

Figure 6.18 : Typical stress - strain data for P(DMAEMA-co-HEMA) hydrogels after equilibrium swelling in buffer solutions. pH of the solutions are already indicated in the figure. HEMA mol%: 10 (●), 20 (○), 30 (▲), 40 (△), 50 (▼), 60 (▽), 70 (■), 80 (□), 90 (◆), 100 (◇).

The elastic modulus of P(DMAEMA-co-HEMA) hydrogels changes depending on the pH of the swelling medium. In acidic pH region, the elastic moduli of hydrogels increase slightly with increasing pH from 2.1 to 7.7. A sharp increase in the elastic moduli of hydrogels was also observed in a narrow range of pH between 7.7 and 8.0 which corresponds to the pH-dependent volume transition of P(DMAEMA-co-HEMA) copolymeric hydrogels as can be seen in Figures 6.13 and 6.14. In basic pH region, the elastic moduli of hydrogels did not change with increasing pH, however, were greater than that of in acidic pH region.

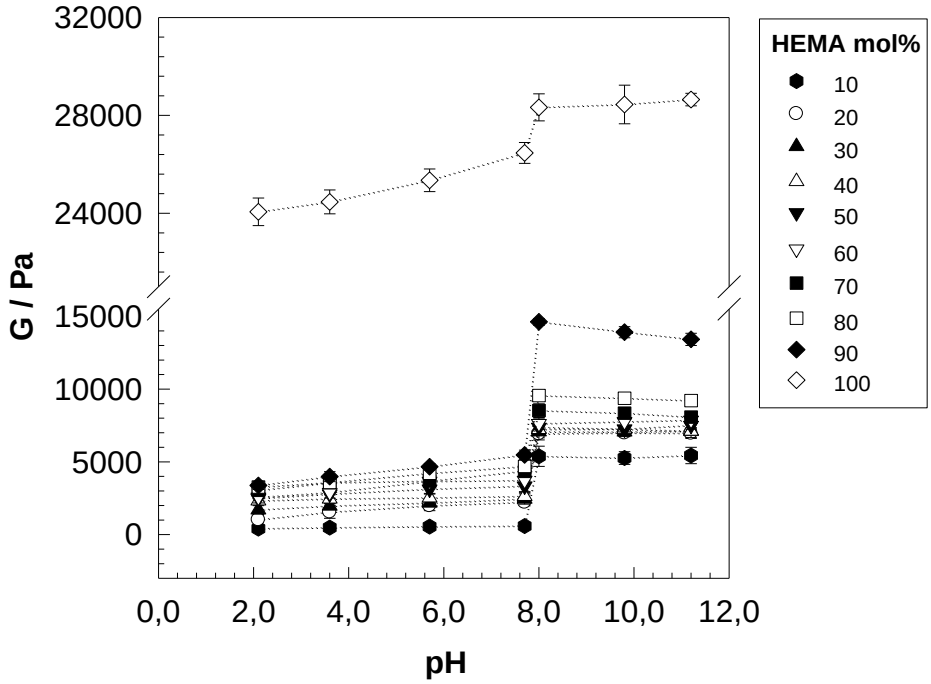

Figure 6.19 : Compression moduli after equilibrium swelling in buffer solutions *G* of P(DMAEMA-co-HEMA) copolymeric hydrogels shown as a function of pH at 25 ^{o}C. The comonomer HEMA content (HEMA mol%) are already indicated in the figure.

In Figure 6.20(A) the elastic moduli *G* of P(DMAEMA-co-HEMA) copolymeric hydrogels and after equilibrium swelling in buffer solution of pH 2.1 (filled symbol) and that of in pH 8.0 (open symbol) were shown as a function of the comonomer HEMA content. An increase in pH led to a decrease in the ionization of the network and reduced the swelling of the hydrogel, and hence to an increase in the modulus. As it can be seen in figure 6.20(B), the volume fraction of crosslinked polymer after equilibrium swelling ν_2 in buffer solution of pH 2.1 also increase with HEMA content. Since the P(DMAEMA-co-HEMA) copolymeric hydrogels remain in the swollen state in pH 2.1, the elastic moduli of hydrogels are lower than that of in pH 8.0. The copolymeric hydrogels exhibit greater elastic moduli in pH 8.0 since they are in collapsed state over the entire range of the HEMA content.

It was also observed that the elastic modulus of P(DMAEMA-co-HEMA) hydrogels changes depending on the comonomer HEMA content used in the preparation. As can be seen, in a particular pH, increasing the HEMA content of the hydrogels increases the value of G. In the solution of pH 2.1, the elastic moduli *G* of hydrogels increase rapidly with increasing HEMA content up to 40 mol% of HEMA. Then, the elastic moduli increase slightly in the range of HEMA between 40 and 90 mol%.

This result is attributed to the effective crosslink density distribution within the polymer matrix and the role of cross-links.

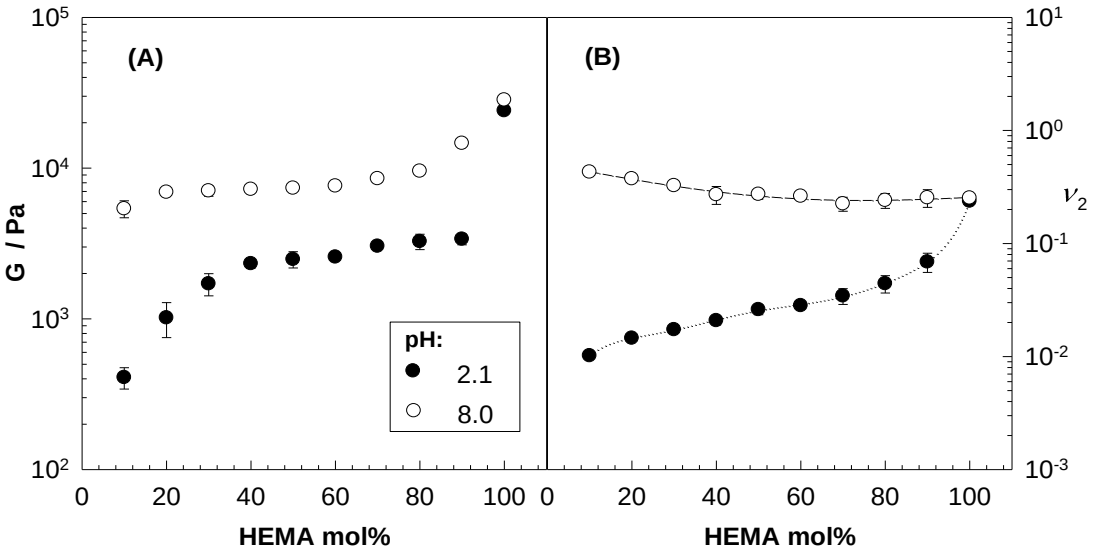

Figure 6.20 : (A) Elastic moduli *G* of P(DMAEMA-co-HEMA) copolymeric hydrogels and (B) the volume fraction of crosslinked polymer after equilibrium swelling ν_2 in buffer solution of pH 2.1 (filled symbol) and that of in pH 8.0 (open symbol) shown as a function of the comonomer HEMA content.

For P(DMAEMA-co-HEMA) hydrogels, using the G and ν_2^0 values the effective crosslink density ν_e of copolymer hydrogels were calculated and the results were collected in Table 6.3. The addition of a small fraction of HEMA led to a significant increase in the effective crosslink density of P(DMAEMA-co-HEMA) hydrogels. For copolymer hydrogels containing 10 mol% of HEMA, ν_e is about 3.81 mol / m^3 while it is 11.48 mol / m^3 for copolymer hydrogels containing 40 mol% of HEMA. Table 6.3 also shows the influence of HEMA content on the swelling ratio and the mechanical properties including compression moduli G of P(DMAEMA-co-HEMA) copolymer hydrogels, and *N* values found from the uniaxial compression experiments in pH 2.1 solutions.

It can be seen that with the increase of HEMA content in copolymers, both the volume fraction of crosslinked polymer after equilibrium swelling and the swelling ratio decrease while the elastic moduli increase. Thus, hydrogels based on DMAEMA with satisfied comprehensive properties can be obtained through carefully selecting the experimental conditions. Previous work of Hariharan and

Peppas showed that the incorporation of HEMA comonomer in the structure of Poly(diethylaminoethyl methacrylate-co-hydroxyethyl methacrylate) hydrogels increases the mechanical strength [65].

Table 6.3 : The composition and characteristic data of P(DMAEMA-co-HEMA) copolymeric hydrogels. ν_2^0 = the volume fraction of crosslinked polymer after the gel preparation, ν_2 = the volume fraction of crosslinked polymer after equilibrium swelling, G = the elastic modulus of gels after their equilibrium swelling in pH 2.1, N = the number of segments between two successive crosslinks of the network, ν_e = the effective crosslink density, χ = the polymer network–solvent interaction parameter in pH 2.1 and at 25 ^{o}C. The numbers in parenthesis are the standard deviations of the separate measurements.

DMAEMA mol%	**HEMA mol%**	ν_2^0	ν_2	**G / Pa**	N	ν_e **(mol/m^3)**	χ
90	10	0.2765	0.0102	408 (66)	14588	3.81	0.475
80	20	0.2730	0.0145	1016 (265)	8160	6.82	0.470
70	30	0.2695	0.0173	1708 (286)	5627	9.87	0.464
60	40	0.2660	0.0208	2326 (152)	4839	11.5	0.468
50	50	0.2625	0.0260	2483 (306)	5527	10.1	0.482
40	60	0.2590	0.0282	2573 (107)	5628	9.87	0.486
30	70	0.2555	0.0344	3036 (106)	5652	9.83	0.493
20	80	0.2520	0.0442	3262 (381)	6580	8.44	0.503
10	90	0.2484	0.0688	3381 (282)	9597	5.79	0.519
0	100	0.2449	0.2369	24059 (563)	4518	12.3	0.593

It was found that an increase in pH leads to an increase in the modulus and also an increase in the crosslinking ratio decreased the modulus due to decreased flexibility of the polymer chains. Horkay et al. [37] studied the elastic shear modulus G and the swelling pressure of pH-responsive hydrogels synthesized by hydroxypropyl methacrylate and *N*,*N*-dimethylaminoethyl methacrylate with crosslinker tetraethylene glycol dimethacrylate. It was reported that the elastic shear modulus G values monotonically increase with the polymer weight fraction in the gel at fixed pH. However, at fixed swelling degree, G increases with decrease in pH (i.e., increase in degree of ionization). Thus the hydrogel stiffens as it swells in response to pH change. One possible explanation for this trend is chain stiffening due to finite chain extensibility, which is more significant at lower pH. In Figure 6.21, photographs of PDMAEMA (left panel) and that of P(DMAEMA-co-HEMA) copolymeric hydrogel containing 30 mol% of HEMA (right panel) during the compression tests after equilibrium swelling in the solution of pH 2.1 were given.

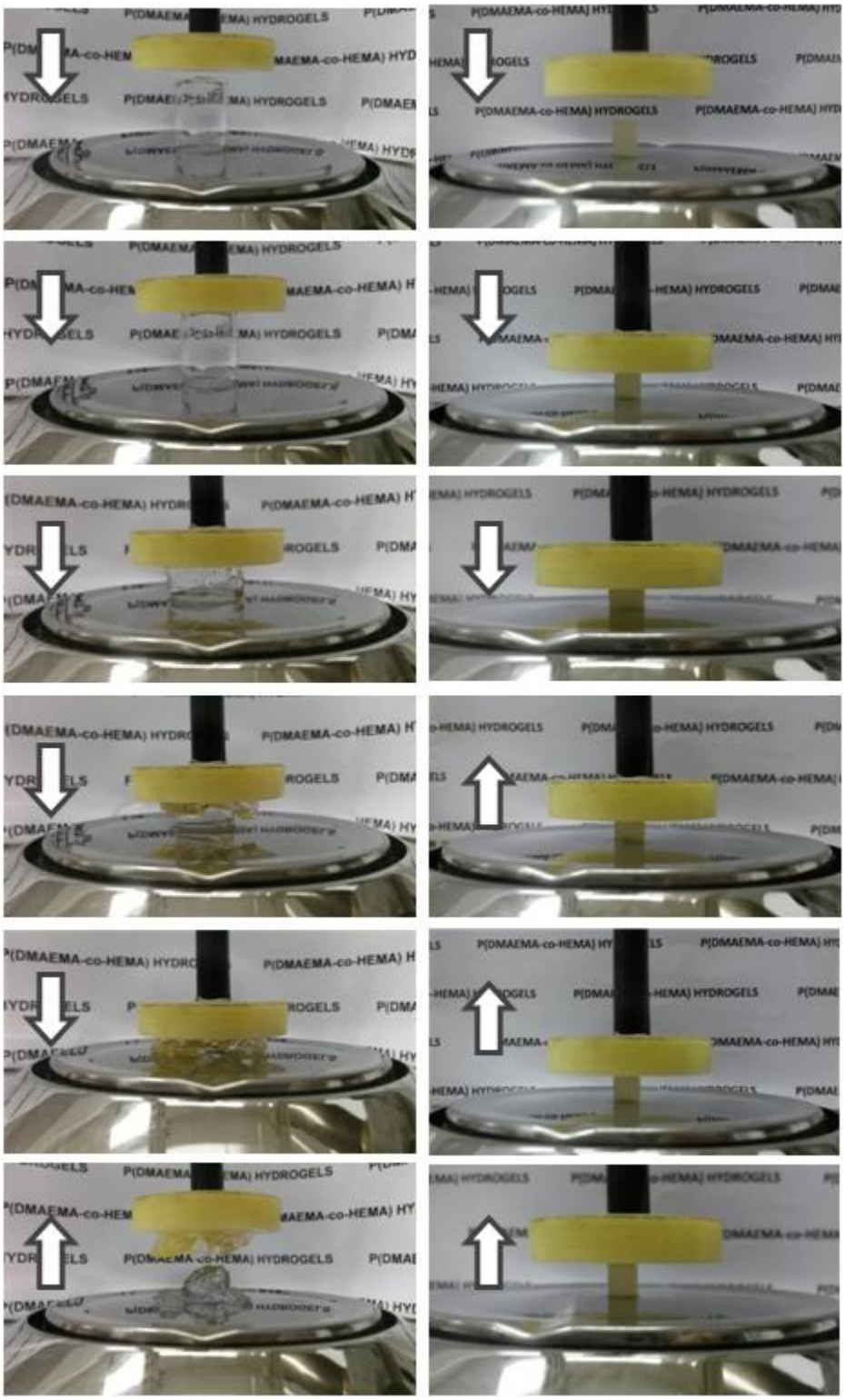

Figure 6.21 : Photographs of PDMAEMA (left panel) and that of P(DMAEMA-co-HEMA) 30 mol% copolymeric hydrogels (right panel) during the compression tests after equilibrium swelling in the solution of pH 2.1.

P(DMAEMA-co-HEMA) copolymeric hydrogels exhibit a high modulus of elasticity when compared with homopolymeric PDMAEMA hydrogels (Fig. 6.13), they were tough and can be compressed up to about 90% strain without any crack development.

However, PDMAEMA hydrogels break at a strain of about 80%. As shown in the left panel, the swollen PDMAEMA homopolymeric hydrogels fractured under low deformation suggesting that cracks develop easily in the gel. This may be due to the fact that the polymer was completely ionized at this pH, and the network chains had greater mobility. However, P(DMAEMA-co-HEMA) copolymeric hydrogel containing 30 mol% of HEMA remained mechanically stable up to about larger compression (right panel of Fig.6.21). After the release of the load, it was observed that the hydrogel sample immediately recovers its original shape, which definitely contributes to the excellent mechanical properties.

6.2.5 Diffusion characteristics of P(DMAEMA-co-HEMA) copolymeric hydrogels

Since the composition of the copolymer determines the concentration of ionizable DMAEMA groups within the network structure which controls the swelling behavior, the diffusion characteristics of P(DMAEMA-co-HEMA) hydrogels for water were studied at various pH values. Figure 6.22 shows the curves of the dynamic swelling process of the hydrogels in buffer solution of pH 2.1. Three characteristic regions were distinguished in all of the swelling curves presented in Figure 6.22. Following the beginning of swelling, linear, non-linear, and plateau regions were consecutively observed. All hydrogels readily swell in acidic medium and the swelling process is faster in the first 70 min and then becomes slower until the hydrogel reaches the equilibrium maximum swelling ratio, at about 100 min. The data of the figure showed that the comonomer HEMA content in the copolymer structure affected the dynamic water uptake to a significant extent. Both the swelling ratio and the swelling rate decreased with increasing amount of the comonomer content. P(DMAEMA-co-HEMA) hydrogels containing greater amount of HEMA (90-100 mol%) exhibit lower swelling ratios. An increase in the HEMA content decreased the water uptake to a considerable extent due to the decrease in free volume available for diffusion of water. It was also shown that the buffer solution had no effect on the water uptake of the PHEMA sample since PHEMA is a non-ionic polymer. To illustrate the swelling kinetics of P(DMAEMA-co-HEMA) hydrogels, the photographs of P(DMAEMA-co-HEMA) hydrogel sample containing

30 mol% HEMA during dynamic swelling at 25°C in pH 2.1 buffer solution are given in Figure 6.23.

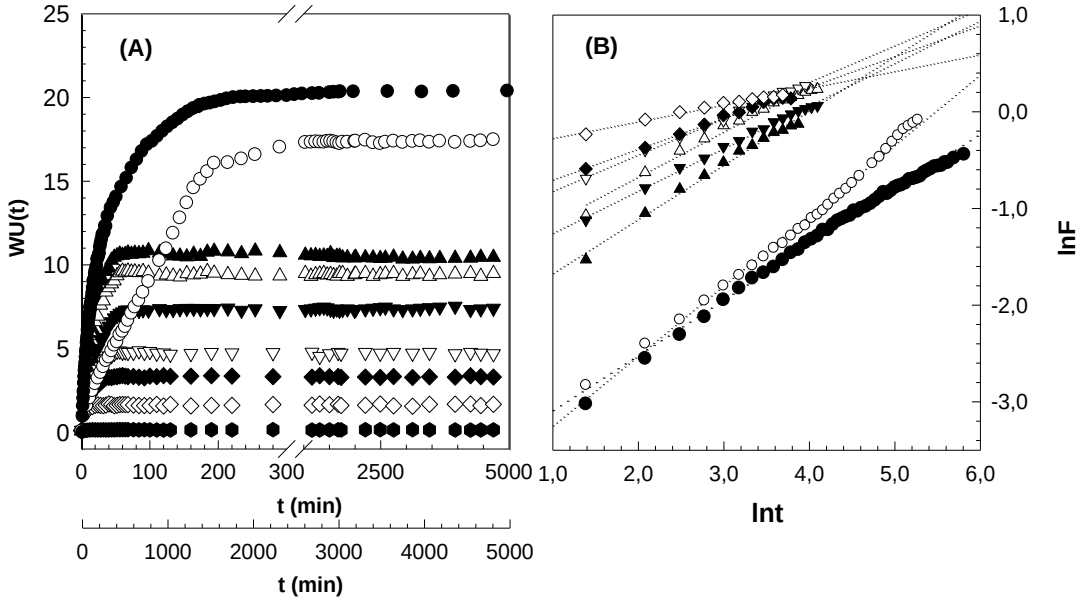

Figure 6.22 : (A) Dynamic water uptake of P(DMAEMA-co-HEMA) hydrogels with different HEMA content in acidic medium (pH = 2.1) as a function of time. The outer axis shows the time scale of hydrogel containing 20 mol% HEMA (B) lnF versus lnt curves of P(DMAEMA-co-HEMA) hydrogels. HEMA mol%: 20 (●), 30 (○), 40 (▲), 50 (△), 60 (▼), 70 (▽), 80 (◆), 90 (◇),100 (●).

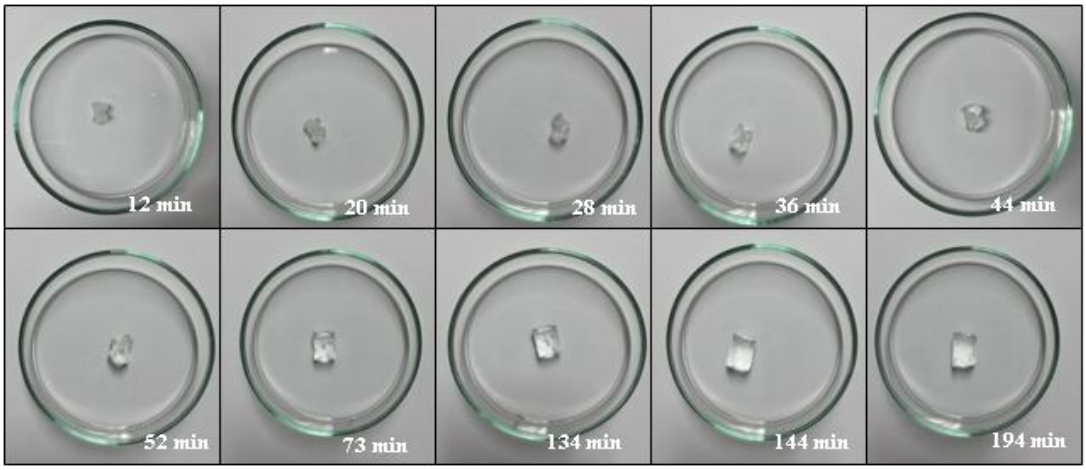

Figure 6.23 : The photographs of a P(DMAEMA-co-HEMA) copolymeric hydrogel sample containing 30 mol% HEMA at 25°C in pH 2.1 buffer solution.

In order to describe the kinetics of hydrogel swelling, the empirical equation given by Ritger and Peppas, so-called power law equation, was used according to Eq. (3.24). Only the data fulfilling the condition $WU(t)/SR(eq) \leq$ 0.6 were taken into

account and Eq. (3.24) was applied to the initial swelling of the curves and the constants *k* and *n* were determined from the intercept (ln*k*) and slope (*n*) of lnF versus lnt plot of the hydrogels given in Figure (6.22)(B) [111-114]. For water uptake of P(DMAEMA-co-HEMA) hydrogels in the solution of pH 2.1, the values of diffusion constant *k* and diffusional exponent *n* as well as the correlation coefficient r^2 are tabulated in Table 6.4. It is clearly seen that the values of *n* for the copolymeric hydrogels in buffer solutions of pH 2.1 are in the range of 0.32 - 0.57. For the hydrogels containing HEMA below 40 mol%, *n* values are found to be slightly over 0.50 and the diffusion of water into hydrogels was taken as a non-Fickian type (anomalous diffusion). This behavior is generally explained as a consequence of a slow relaxation rate of the polymer matrix and reveals the existence of certain coupling between molecular diffusion and tension relaxation developed during swelling of the hydrogels. If HEMA mol% increases from 50 to 80, *n* values range between 0.47 and 0.32 manifest that the diffusion behavior of water in these hydrogels follows the Less Fickian mechanism and the dominant physical mechanism controlling the water uptake of these copolymeric hydrogels is diffusion according to the classification of the relative rates of diffusion and polymer relaxation proposed by Alfrey et al. [115]. The diffusion coefficient values of water moving through the P(DMAEMA-co-HEMA) hydrogels were determined from the following equation, and the results were summarized in Table 6.4:

$$D = \pi l^2 \left(\frac{k}{4} \right)^{1/n} \qquad \textbf{(6.10)}$$

where *D* is the diffusion coefficient (cm^2/s) and *l* is the initial dry diameter of the hydrogel. It was observed that the diffusion coefficient of hydrogels *D* decreases with an increase of HEMA content in the hydrogel. This is explained by the restriction of the expansion of the network structure resulting from the increase of the comonomer concentration and the crosslinking density as can be seen in Table 6.3. The incorporation of HEMA into DMAEMA gel would diminish water to penetrate into the gel and the penetration of water into the gel becomes more difficult. It is well known that the diffusion coefficient of solutes in the hydrogel is dependent on a number of factors, such as, the temperature, the structure and mesh size of the polymeric network, the polymer-solute interaction dictated by monomer

composition, the degree of swelling, and the nature/size of the solute. The diffusion coefficients of P(DMAEMA-co-HEMA) hydrogels were found in the range of 2.15 - 4.16x10^{-6} cm^2/s, all falling well within that which is typical for solute diffusion coefficients (10^{-6}-10^{-7} cm^2 /s) in rubbery polymers [116].

Table 6.4 : Initial diffusion coefficient of water *D*, kinetic exponent *n* and characteristic constant *k* of water penetrated through copolymeric hydrogels obtained from fitting experimental data to Ritger-Peppas model.

%HEMA	*n*	ln*k*	*k*	r^2	D (cm^2/s)
20	0.5723	-3.665	0.0256	0.9933	4.16 x 10^{-6}
30	0.5726	-3.977	0.0187	0.9934	3.49 x 10^{-6}
40	0.5722	-2.261	0.1042	0.9932	3.08 x 10^{-6}
50	0.4673	-1.610	0.1999	0.9825	2.73 x 10^{-6}
60	0.4398	-1.698	0.1829	0.9964	2.54 x 10^{-6}
70	0.3765	-1.198	0.3016	0.9967	2.21 x 10^{-6}
80	0.3294	-1.024	0.3590	0.9928	2.15 x 10^{-6}

The diffusion coefficient of water was also found to depend on DMAEMA content in the network matrix. As the DMAEMA mol% in the copolymer structure was increased, there was a corresponding increase in the diffusion coefficient. This phenomenon can be explained by considering the greater extent of protonation of pendant amine groups in the hydrogels produced with higher DMAEMA concentration resulting in a greater influx of water into the hydrogel matrix and the development of charge on the polymer backbone causes the hydrogel to swell allowing the water to diffuse into it.

Similar results were reported by Tuncel and Cicek for poly(HEMA-co-DMAEM) copolymer gels produced by a copolymerization initiated by potassium persulfate in an aqueous medium [117]. They applied an unsteady state diffusion model on the dynamic behavior of HEMA-DMAEM gels and the effective diffusion coefficients for water were obtained in a very broad range between 1x10^{-8} and 1x10^{-5} cm^2/s depending on the copolymer composition. The swelling and shrinking diffusion coefficients in the acidic pH region were mostly greater than 1x10^{-6} cm^2/s and increased with the increasing DMAEM content of the copolymer. Lee and Yeh [118] prepared a series of thermoreversible copolymeric hydrogels with N-isopropylacrylamide and hydrophobic monomers and observed that the equilibrium

swelling ratio decreased, but the gel strength increased with an increase of the content of hydrophobic monomer. The investigation of water diffusion indicated that the swelling exponents and *D* values for the copolymeric gels decreased with an increase of hydrophobic monomer content. Brahim et al. [92] synthesized P(HEMA-DMAEMA) hydrogels containing 3-(trimethoxy-silyl) propylmethacrylate and investigated the release profiles for insulin and protamine with respect to variation in the pH of the bathing medium as well as the DMAEMA content. It was observed that the hydrogels exhibited classical Fickian diffusion release profiles and the dominant physical mechanism controlling drug release from these hydrogels is diffusion. As the DMAEMA content of the hydrogel was increased from 0 to 20 mol %, there was a corresponding increase in drug diffusion coefficient. This differential release confirms the role of internal protonation in effecting the greater release of the protonated drug molecule. The cationic hydrogels based on poly(diethylaminoethyl methacrylate-co-hydroxyethyl methacrylate) P(DEAEm-co-HEMA) were also synthesized by Hariharan and Peppas [65]. The *n* values of hydrogels indicated that the water uptake in polymer samples containing 10 mol% DEAEM followed Fickian transport, whereas for samples containing 30 mol% DEAEM, the *n* values at pH 2 indicated that the ionization of the network and the resultant swelling of the polymer caused the relaxation process to dominate over diffusion.

The effect of DMAEMA content on the deswelling kinetics of P(DMAEMA-co-HEMA) hydrogels was also studied when the swollen hydrogels were transferred from acidic medium at pH 2.1 into pH 8.0 medium as shown in Figure 6.24. It can be seen that all hydrogels exhibit fast response rate to changing pH than that of the pure PHEMA hydrogel. P(DMAEMA-co-HEMA) hydrogels containing 20 mol% of HEMA loses more than 90% water within 60 min, and it needs more than 3 h to reach the deswelling equilibrium. This retardation may be attributed to the formation of a skin layer on the surface of the hydrogels, which effectively hinders the water molecules releasing from the inner of the network structure [119]. The variation of swelling and shrinking diffusion coefficients of P(NIPAM-*co*-HEMA) gels with the HEMA content of the copolymer was studied and it was found that the HEMA content of copolymer did not significantly affect the swelling and shrinking diffusion coefficients in the temperature range of 4–20 ^{o}C. Only a slight decrease was

observed in the swelling and shrinking diffusion coefficients with the increasing HEMA content of the copolymer gel [120].

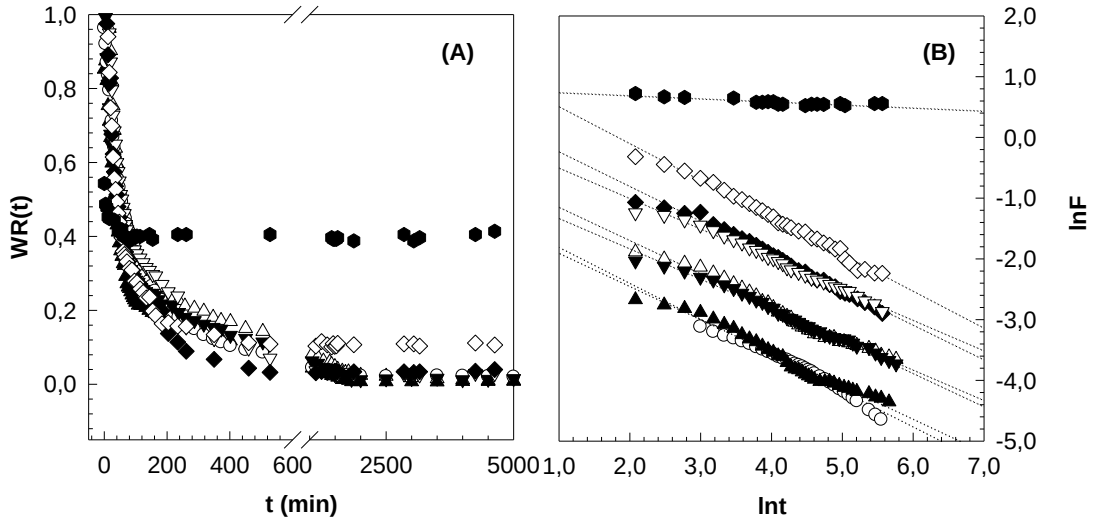

Figure 6.24 : (A) Deswelling kinetics of P(DMAEMA-co-HEMA) hydrogels with different HEMA content in buffer solution at pH 8.0 as measured from an equilibrium swelling condition in pH 2.1. (B) lnF versus lnt curves of P(DMAEMA-co-HEMA) hydrogels. HEMA mol%: 30 (○), 40 (▲), 50 (△), 60 (▼), 70 (▽), 80 (◆), 90 (◇), 100 (●).

6.3 Ion-stimulus response of P(DMAEMA-co-HEMA) copolymeric hydrogels

The influences of ionic strength of salt solutions on the swelling behavior and mechanical properties of the P(DMAEMA-co-HEMA) hydrogels were also examined. Ion-stimulus-responsive swelling and elasticity of the copolymers was studied in aqueous NaCl, KCl, KBr, KI, $CaCl_2$, $BaCl_2$ and $MgCl_2$ solutions.

6.3.1 Influence of salts on the equilibrium swelling

The influence of salts on the swelling of P(DMAEMA-co-HEMA) hydrogels in aqueous solutions is of obvious practical interest. In order to determine the effect of salt on water absorbency, two series of salt solutions were used: chlorides with variable cations and potassium salts with different anions. Figure 6.25 shows the equilibrium volume swelling ratio V_{eq} of P(DMAEMA-co-HEMA) hydrogels in monovalent salt solutions of KI (A), KBr (B), KCl (C) and NaCl (D) with concentrations from 10^{-5} to 1 M, respectively. The water absorbency of P(DMAEMA-co-HEMA) hydrogels in divalent salt solutions of $MgCl_2$(A), $CaCl_2$(B)

and $BaCl_2$ (C) was also given in Figure 6.26. The swelling measurements in all types of salt solutions showed that P(DMAEMA-co-HEMA) hydrogels exhibit strong salt-sensitive swelling behavior over the entire range of the comonomer HEMA concentrations.

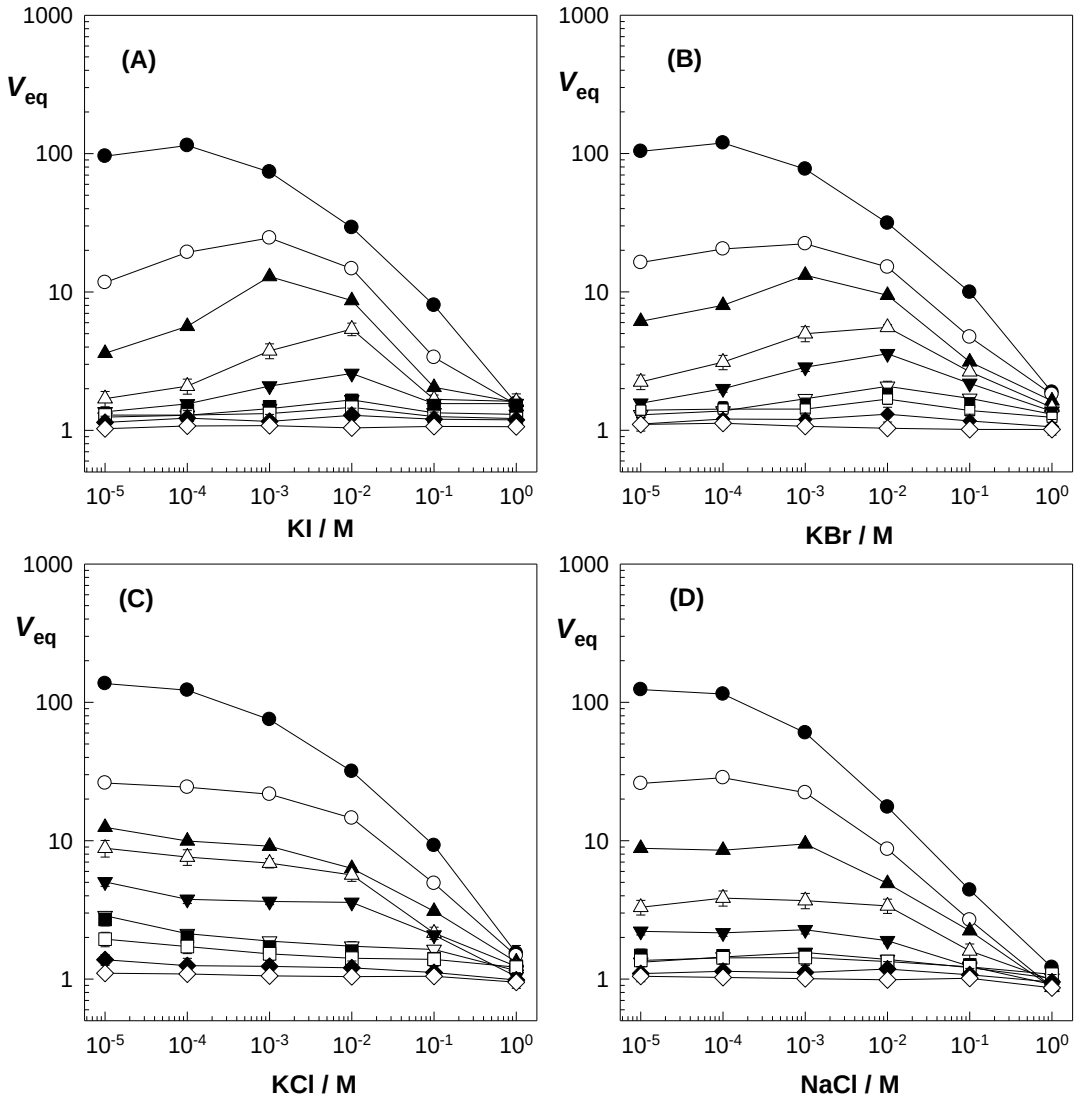

Figure 6.25 : The equilibrium swelling ratio of P(DMAEMA-co-HEMA) hydrogels as a function of the concentration of aqueous salt solutions of KI (A), KBr (B), KCl (C) and NaCl (D). The solid curves only show the trend of the data. HEMA mol%: 10 (●), 20 (○), 30 (▲), 40 (△), 50 (▼), 60 (▽), 70 (■), 80 (□), 90 (◆), 100 (◇).

The swelling of P(DMAEMA-co-HEMA) hydrogels in saline solutions was distinctly decreased when compared to the values measured in deionized water given in part 6.1 and Figure 6.2. It can be seen from the figures that, in the medium range of salt concentration, the swelling ratio of P(DMAEMA-co-HEMA) hydrogels increases with decreased comonomer HEMA concentration in the feed. The

exchange of salt cations in the case of the chlorides as well as the exchange of anions for the potassium salts does not lead to a significant effect on the swelling behavior of the homopolymeric PHEMA gel. In all cases the increase of salt concentration leads to a gel shrinking. Figure 6.27 shows the photographs of P(DMAEMA-co-HEMA) copolymeric hydrogel sample containing 20 mol% HEMA in the feed after equilibrium swelling in aqueous KCl solutions ranging from 10^{-5} to 1.0 M from right to left.

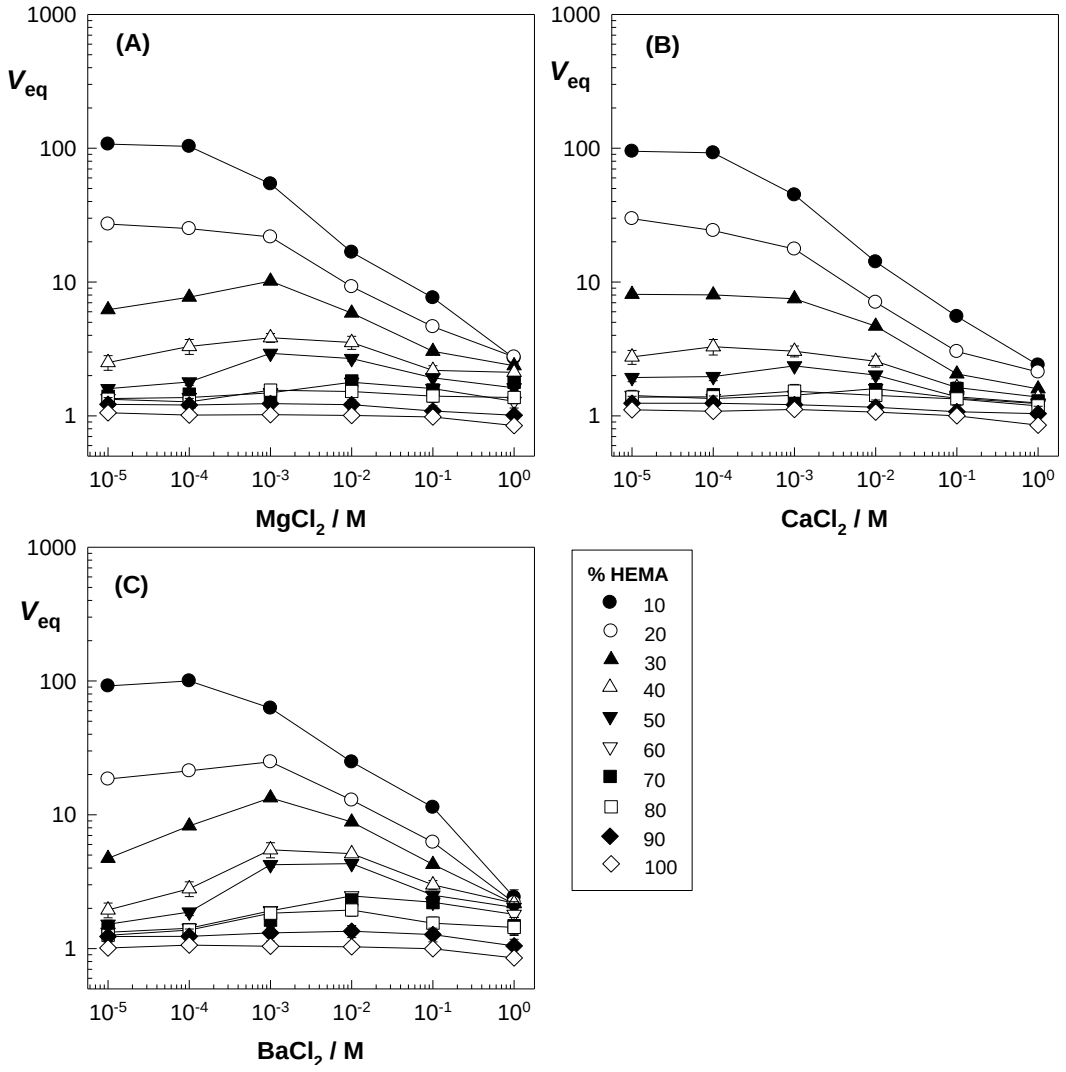

Figure 6.26 : The equilibrium swelling ratio of P(DMAEMA-co-HEMA) hydrogels as a function of the concentration of aqueous salt solution of $MgCl_2$ (A), $CaCl_2$ (B), and $BaCl_2$ (C). The HEMA contents of the hydrogels (HEMA mol%) are already indicated in the figure.

As shown in the Fig. 6.25 and 6.26, the swelling ratio of P(DMAEMA-co-HEMA) hydrogels decreases with increasing salt concentration in the external solution from 10^{-5} to 1.0 M. However, three distinct regions can be described in the salt

concentration dependence of the swelling of P(DMAEMA-co-HEMA) hydrogels: (1) when the salt solution is diluted up to about 10^{-4}-10^{-5} M, the swelling curve of hydrogel samples holds horizontally and the copolymeric hydrogels are in fully swollen state; (2) while the decrease in V_{eq} is rapid up to 10^{-2} M salt concentration; (3) as the salt concentration further increases, the decrease in V_{eq} slows down between 10^{-1} - 1.0 M and the swelling curves also converge together in the concentrated salt solution (1.0 M).

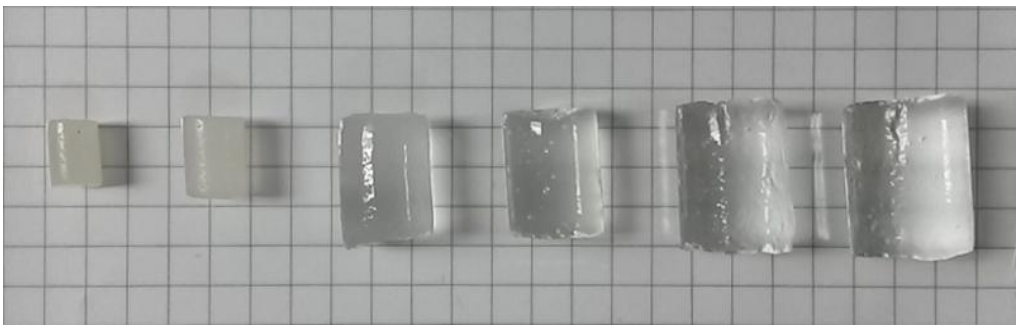

Figure 6.27 : Photographs of P(DMAEMA-co-HEMA) copolymeric hydrogel sample containing 20 mol% HEMA in the feed after equilibrium swelling in KCl solutions ranging from 10^{-5} to 1 M from right to left.

The charged groups attached to the polymer network play an important role in the phenomenon, which could be interpreted by Donnan equilibrium theory [121]. This phenomena can be attributed to the electrostatic repulsion between charged groups on the network chains and to the concentration difference of mobile ions inside the hydrogel and the external solution governed by the Donnan potential. During the swelling of P(DMAEMA-co-HEMA) hydrogels in salt solutions, the mobile counterion concentration in the external solution is higher than that of in the gel phase, which results in an osmotic pressure that water molecules flow from the gel to the solution phase so that P(DMAEMA-co-HEMA) hydrogels deswell as observed. In Figure 6.25A-B and Figure 6.26A-C, for the polymer network with low comonomer HEMA content, the swelling ratio could be divided into two stages: an increase of swelling ratio for some extent, followed by a continuous shrinkage with increased salt concentration. The first increase in the swelling ratio could be explained by the increased osmotic pressure of counterions in the gel phase due to the addition of salt to the system. Another result obtained from Figure 6.26 is that quite concentrated (>1.0 M) salt solutions would be required to make these gels behave like an uncharged one since DMAEMA is a weak electrolyte.

Figure 6.28 shows the equilibrium swollen volume V_{eq} of P(DMAEMA-co-HEMA) hydrogels in two series of the different types of salts: potassium salts with different anions (A) and chlorides with variable cations (B). The effect induced by the co-ion species of a series of potassium salts was monitored and the swelling curves of hydrogels containing 10 and 20 mol% HEMA in salt solutions having the same cation K^+ and different co-ions were shown in Figure 6.28(A). It was found that the salt-dependent swelling ratio of hydrogels is decreased with HEMA concentration in the feed increased up to 20 mol% and in the series of alkali halides, the efficiency of lowering V_{eq} follows the ranking I < Br < Cl at the same ionic strength. In Figure 6.28(B), the swelling curves of P(DMAEMA-co-HEMA) hydrogels containing 10 mol% HEMA in the feed are given in the salt solutions with different counterions K^+, Na^+, Mg^{2+}, Ba^{2+} and Ca^{2+}. The co-ions in the salts are identical in each hydrogel; i.e., $C1^-$. Since these mobile ions must remain inside the hydrogel for the maintenance of electroneutrality, the electrostatic interaction and the colligative property caused by the mobile ions inside the hydrogel will be important in the swelling while the other network parameters are identical for all the samples.

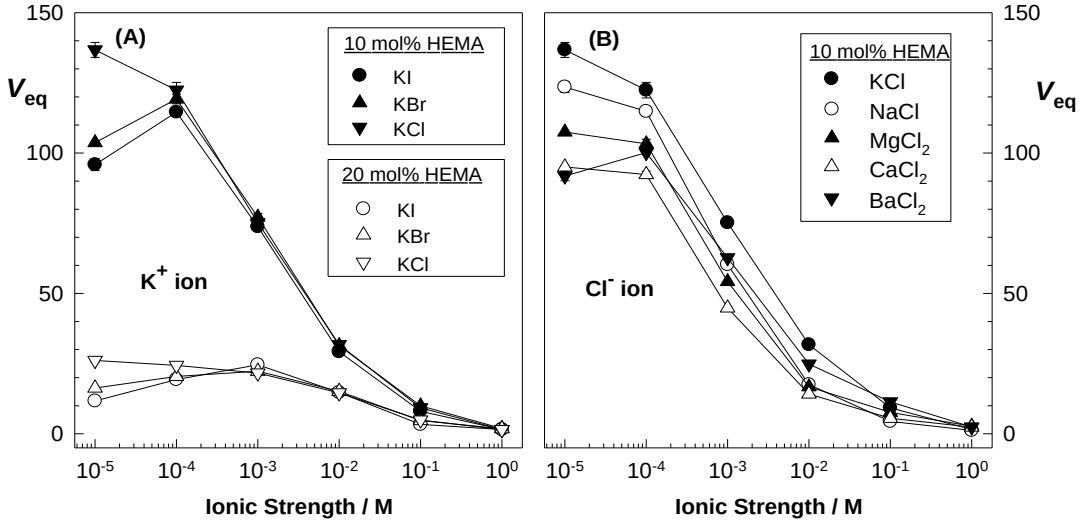

Figure 6.28 : (A) Swelling curves of P(DMAEMA-co-HEMA) hydrogels containing 10 mol% HEMA (solid symbols) and 20 mol% HEMA (open symbols) in salt solutions with the same cation K^+ and different anions. (B) Swelling curves of P(DMAEMA-co-HEMA) hydrogels containing 10 mol% HEMA in chlorides with variable cations, showing the dependence on the counterion species K^+, Na^+, Mg^{2+}, Ba^{2+} and Ca^{2+}.

The essential difference between an anion and a cation could be in manner in which they interact with water. The lower the salt concentration, the higher the cation valence, the less the radius of the same valance cation, the more the salt solution absorbencies. By the increase in ions size, the salt-dependent swelling ratio of hydrogels decrease due to the difficulty in the penetration of these ions into the hydrogel networks. Since the distribution in the concentration of mobile ions between the gel and solution phase is reduced by increasing the ionic strength, the decreasing osmotic swelling pressure of the mobile ions inside the gel also lead to a decrease in the salt-dependent swelling ratio. The swelling curves of P(DMAEMA-co-HEMA) hydrogels containing 10 mol% HEMA against the ionic strength in the salt solutions were also collected in Figure 6.29.

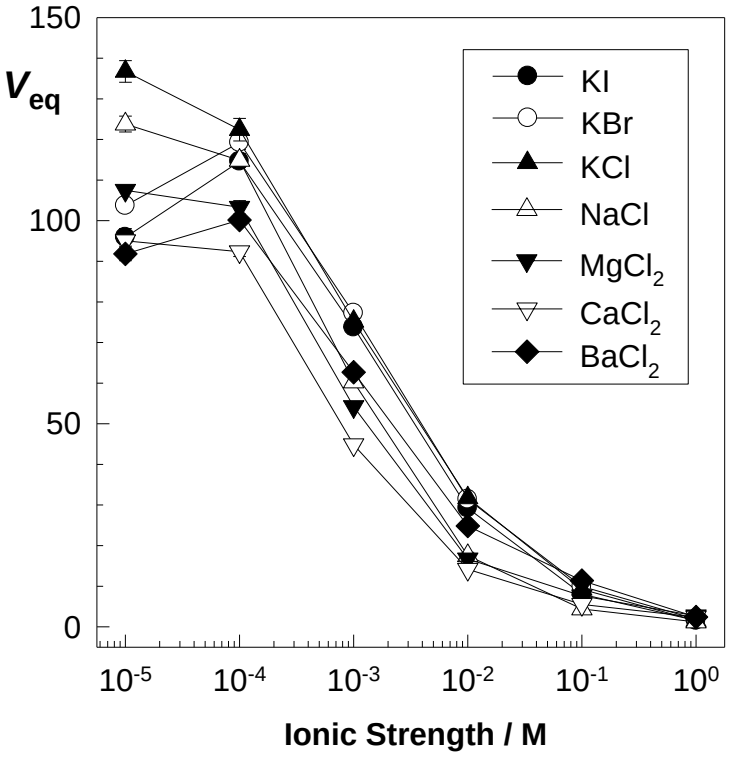

Figure 6.29 : Swelling curves of P(DMAEMA-co-HEMA) hydrogels containing 10 mol% HEMA in the feed plotted against the ionic strength in the seven salt solutions as indicated.

When comparing the swelling ratios for one gel with different counterions, one can find its decrease with counterion change in the order of K^+, Na^+, and Mg^{2+}, Ba^{2+} and Ca^{2+}, irrespective of the co-ions Cl^- , Br^- and I^-. At higher ionic strenght, the swelling curves of hydrogels in salts having univalent cations Na^+ and K^+ merge into one.

6.3.2 Elasticity of P(DMAEMA-co-HEMA) hydrogels in salt solutions

To reveal the effect of salt on the elasticity of P(DMAEMA-co-HEMA) copolymeric hydrogels, uniaxial compression measurements were performed on hydrogel cylinders at equilibrium with salt solutions. The deformation as a function of the applied force was measured and the elastic modulus, G_{salt}, was calculated from the nominal stress, *F* (force per unit undeformed cross-section). In Figure 6.30, the stress - strain data of P(DMAEMA-co-HEMA) hydrogel containing 20 mol% HEMA in the feed after equilibrium swelling in different salt solutions was given. The ionic strength of the solutions are already indicated in the figure. Although the comonomer HEMA content of P(DMAEMA-co-HEMA) hydrogels is the same, the slope of the stress-strain isoterms varies depending on the type of the salt and also the ionic strength of the solutions. In Figure 6.31, the photographs of P(DMAEMA-co-HEMA) copolymeric hydrogel sample containing 20 mol% HEMA during the compression tests after equilibrium swelling in 1.0 M NaCl solution are shown.

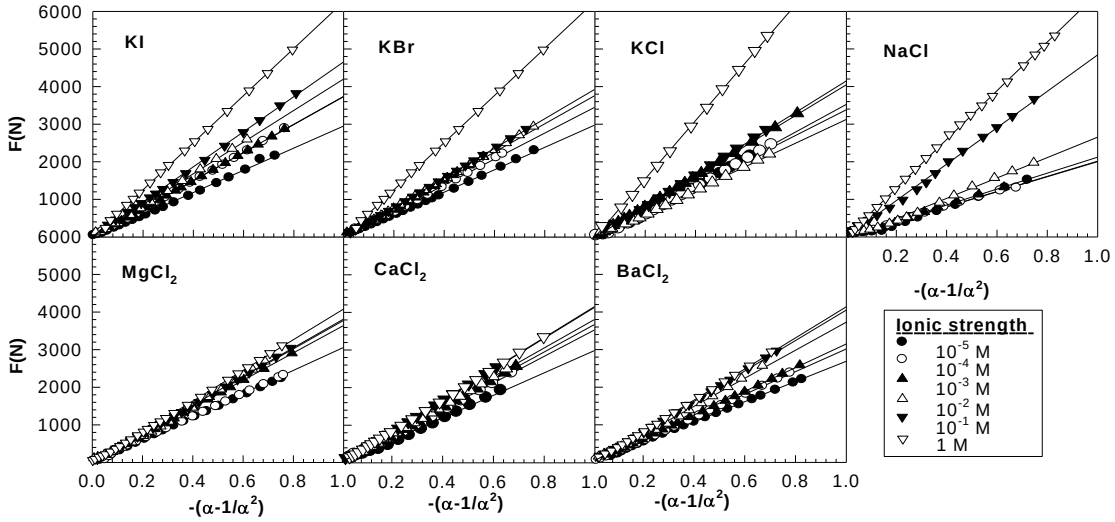

Figure 6.30 : Typical stress - strain data for P(DMAEMA-co-HEMA) hydrogels containing 20 mol% HEMA in the feed obtained from the compression tests after equilibrium swelling in salt solutions. The ionic strength of the solutions are already indicated in the figure.

The gel strength of P(DMAEMA-co-HEMA) hydrogels was evaluated from the stress - strain plots and the results were collected in Figure 6.32 and 6.33. The influence of different type of salts on the elasticity after equilibrium swelling indicated that the elastic modulus of P(DMAEMA-co-HEMA) hydrogels increases as the comonomer HEMA content in the feed increased.

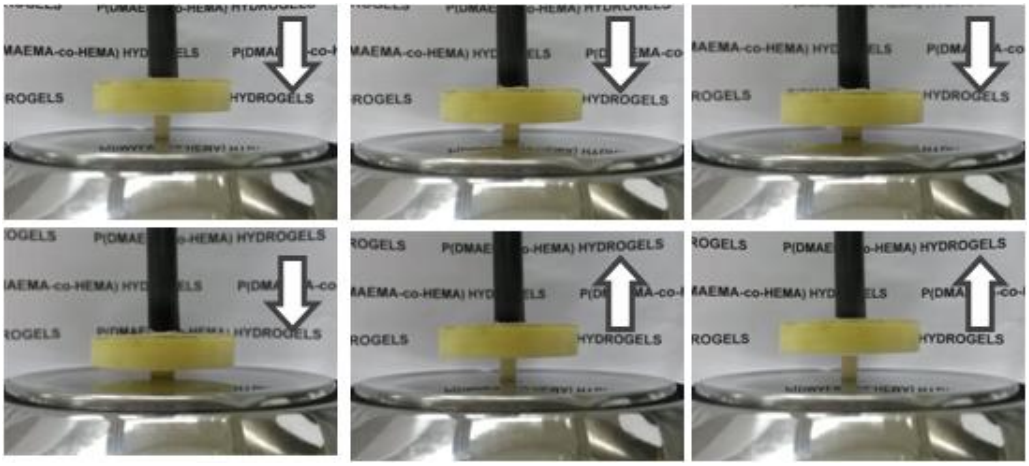

Figure 6.31 : Photographs of P(DMAEMA-co-HEMA) copolymeric hydrogel sample containing 20 mol% HEMA in the feed during the compression tests after equilibrium swelling in 1.0 M NaCl solution.

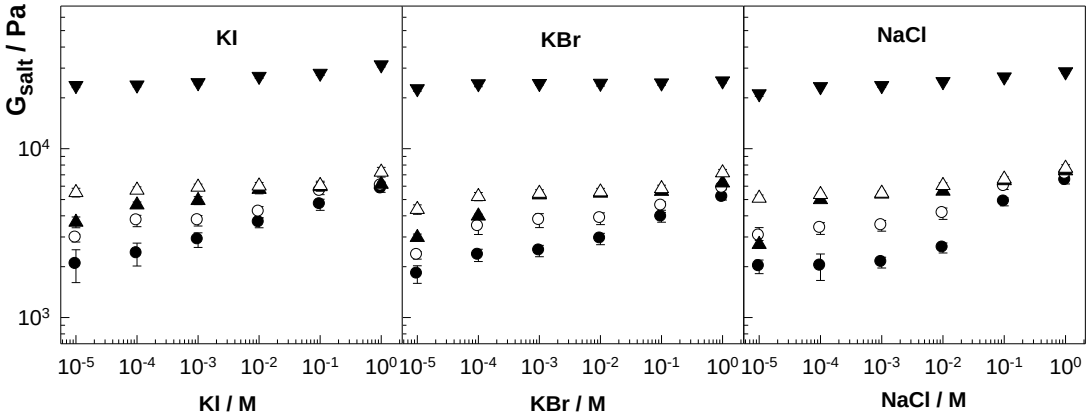

Figure 6.32 : Elastic modulus G_{salt} of P(DMAEMA-co-HEMA) hydrogels after equilibrium swelling in salt solutions of KI, KBr and NaCl shown as a function of the ionic strength. HEMA mol%: 20 (●), 40 (○), 60 (▲), 80 (△), 100 (▼).

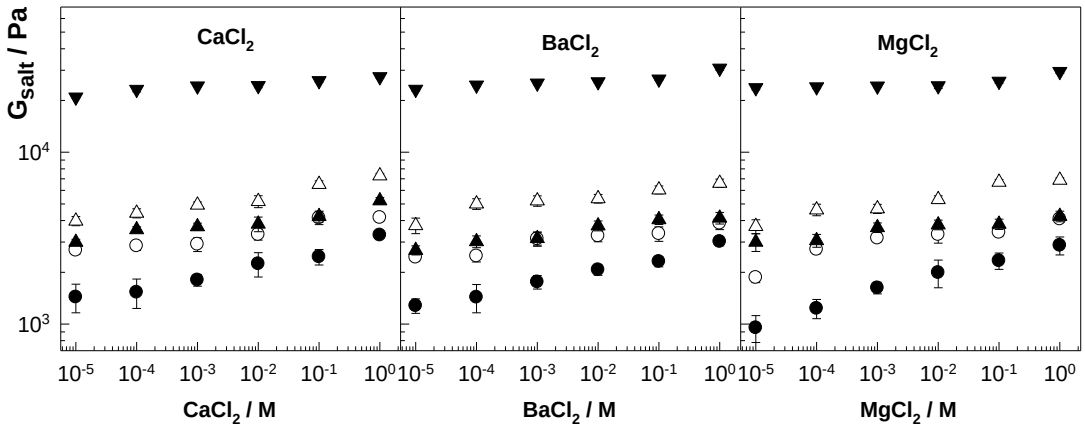

Figure 6.33 : Elastic modulus G_{salt} of P(DMAEMA-co-HEMA) hydrogels after equilibrium swelling in salt solutions of $CaCl_2$, $BaCl_2$ and $MgCl_2$ shown as a function of the ionic strength. HEMA mol%: 20 (●), 40 (○), 60 (▲), 80 (△), 100 (▼).

The elastic moduli G_{salt} data of P(DMAEMA-co-HEMA) hydrogels after equilibrium swelling in seven salt solutions were collected in Table 6.5 as a function of the ionic strength of the salt solutions. The elastic modulus of hydrogels also increases with increasing the ionic strength of the salt solution. As seen in Figure 6.25 and 6.26, the equilibrium swelling ratio of hydrogels decreased with the increase of salt concentration in the external solution which was attributed to the decrease in the concentration difference of counterions inside and outside the hydrogel. The dilution of the salt solution up to 10^{-5} M induces a 3.0 fold decrease in the elastic modulus of hydrogels in NaCl, KBr, KI and KCl solutions whereas 2.5 fold decrease in $CaCl_2$, $BaCl_2$ and $MgCl_2$ solutions is obtained. When the salt solution is diluted, the ions may interact with the side groups of the chains and exhibit ion-bonding property. Therefore, the binding of ions to the P(DMAEMA-co-HEMA) network chains causes an external swelling of the hydrogels which results in decreasing of the elastic modulus. This result can be reflected by the effective crosslink density ν_e and the average network chain length, in terms of the average molecular weight of the network chains between the crosslink points $\overline{M}_c$ which can be given by Eq. (5.9).

By using the G_{salt}, ν_2 and ν_2^0 values of hydrogels; the average molecular weight of the network chains $\overline{M}_c$ and the effective crosslink densities ν_e of P(DMAEMA-co-HEMA) hydrogels were calculated and the results for the phantom network model (ϕ= 4) were collected in Figure 6.34A and B as a function of the ionic strength of the salt solutions. From the comparison of Figures 6.32-6.34, it is seen that $\overline{M}_c$ values of P(DMAEMA-co-HEMA) hydrogels decrease first slightly up to 10^{-3} M, but then increase rapidly with increasing salt concentration. The effective crosslink density values ν_e of hydrogels first increase with increasing salt concentration up to 10^{-3} M and then decrease with further increasing salt concentration.

As discussed previously, the crosslinker DEGDMA with oxyethylene repeating units bears long chain spacer between two vinyl groups and the absorption of water causes the network to expand and force the polymer chains to stretch. As a result, the chains making up the network structure is assumed in a stretched conformation as the polymer network swells. Since the network chains in these swollen hydrogels are in the expanded configuration, the increase of the elastic modulus is connected with high stretching of the network chains. In this region, the higher crosslink density may

cause stronger thermodynamic force which makes water to diffuse faster and results in a higher rate of swelling.

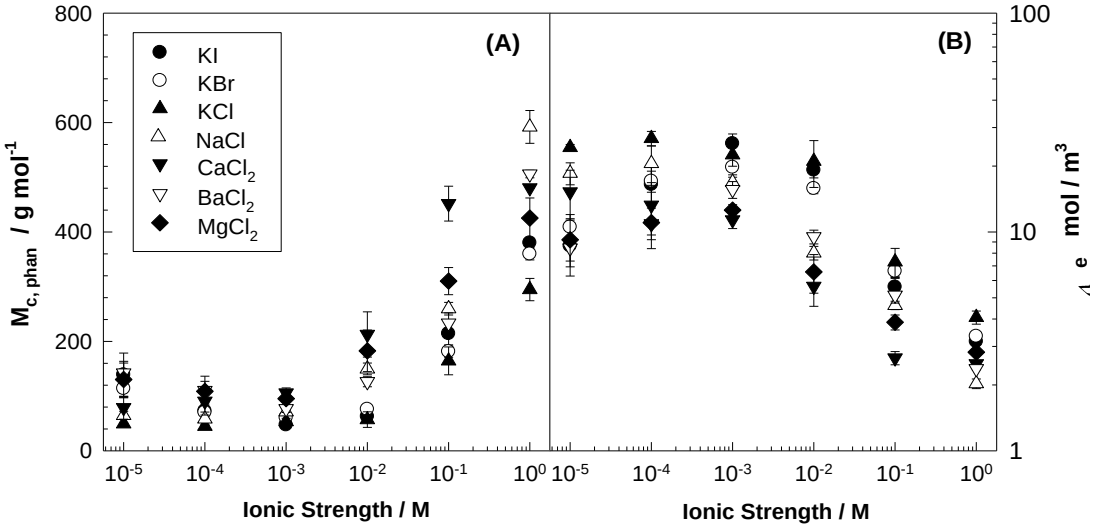

Figure 6.34 : The average molecular weight of the network chains $M_{c,phan}$ (A) and the effective crosslink density ν_e of P(DMAEMA-co-HEMA) hydrogels containing 20 mol% HEMA in the feed shown as a function of the ionic strength of the salt solutions.

By using the experimentally determined equilibrium swelling ratios and $\overline{M}_c$ values, the interaction parameter χ of the P(DMAEMA-co-HEMA) – water system was calculated and the results were collected in Table 6.6 for all type of salt solutions. It was found that the χ parameter of P(DMAEMA-co-HEMA) – water system which describes the total interaction between the network and water is dependent on the salt concentration in the range of interest. It is expected that the specific interactions between cations and side groups of polymeric network affect the mixing term of the free energy. The low value of χ parameters between the P(DMAEMA-co-HEMA) network and water in diluted range of the salt solutions means a strong interaction between the polymer and water and a weak interaction between hydrophobic groups of the polymer chains.

Table 6.5 : The elastic modulus G_{salt} of (DMAEMA-co-HEMA) hydrogel containing 20 mol% HEMA in the feed after equilibrium swelling in salt solutions. The standard deviations of the separate measurements are also given.

Conc.	NaCl	KBr	KI	KCl	$CaCl_2$	$BaCl_2$	$MgCl_2$
M	G / Pa	G / Pa	G / Pa	G / Pa	G / Pa	G / Pa	G / Pa
1	6481 ± 298	5145 ± 181	5776 ± 234	5749 ± 126	3290 ± 82	3017 ± 243	2868 ± 345
10^{-1}	4844 ± 262	3932 ± 261	4666 ± 342	4157 ± 162	2460 ± 254	2308 ± 156	2335 ± 254
10^{-2}	2587 ± 176	2926 ± 225	3647 ± 245	2829 ± 143	2239 ± 363	2066 ± 145	1990 ± 365
10^{-3}	2122 ± 156	2483 ± 193	2887 ± 287	2349 ± 135	1802 ± 142	1756 ± 359	1622 ± 125
10^{-4}	2018 ± 359	2340 ± 195	2388 ± 369	2184 ± 259	1529 ± 297	1430 ± 268	1232 ± 158
10^{-5}	2004 ± 185	1810 ± 216	2066 ± 456	1977 ± 147	1433 ± 272	1277 ± 324	950 ± 169

Table 6.6 : The values of the Flory-Huggins interaction parameter for P(DMAEMA-co-HEMA) hydrogels containing 20 mol% HEMA in salt solutions. The standard deviations of the separate measurements are also given in the magnidute of 10^{-3}.

Conc. M	χ (NaCl)	χ (KCl)	χ (KBr)	χ (KI)	χ ($CaCl_2$)	χ ($BaCl_2$)	χ ($MgCl_2$)
1	0.63 ± 1.8	0.57 ± 0.8	0.55 ± 0.9	0.56 ± 2.4	0.54 ± 1.4	0.54 ± 3.3	0.53 ± 1.6
10^{-1}	0.53 ± 0.9	0.50 ± 0.3	0.51 ± 9.4	0.52 ± 0.3	0.53 ± 1.9	0.50 ± 0.2	0.51 ± 1.1
10^{-2}	0.49 ± 0.4	0.42 ± 1.3	0.44 ± 0.3	0.42 ± 3.3	0.50 ± 0.7	0.47 ± 0.9	0.49 ± 1.1
10^{-3}	0.40 ± 4.3	0.39 ± 5.6	0.38 ± 7.4	0.33 ± 8.3	0.45 ± 2.3	0.39 ± 3.4	0.43 ± 0.3
10^{-4}	0.34 ± 1.7	0.34 ± 4.9	0.40 ± 6.8	0.41 ± 1.1	0.41 ± 1.6	0.40 ± 8.3	0.42 ± 7.8
10^{-5}	0.37 ± 9.1	0.35 ± 0.8	0.45 ± 3.4	0.48 ± 4.1	0.37 ± 2.1	0.46 ± 3.5	0.43 ± 1.2

6.3.3 Swelling-shrinking kinetics of P(DMAEMA-co-HEMA) hydrogels in salt solutions

To understand the swelling behavior of P(DMAEMA-co-HEMA) hydrogels in the presence of salts, the dynamic kinetics of swelling/shrinking process have been studied and the results were collected in Figures 6.35 and 6.36. Different mathematical models have been developed to define the swelling and shrinking kinetics of ion-responsive hydrogels and by applying these models, it is possible to estimate the diffusion coefficient of water within the gel matrix. The kinetics of swelling of P(DMAEMA-co-HEMA) hydrogels are shown in Figure 6.35(A), giving the effects of NaCl, KBr, KI, KCl, $CaCl_2$, $BaCl_2$ and $MgCl_2$ solutions.

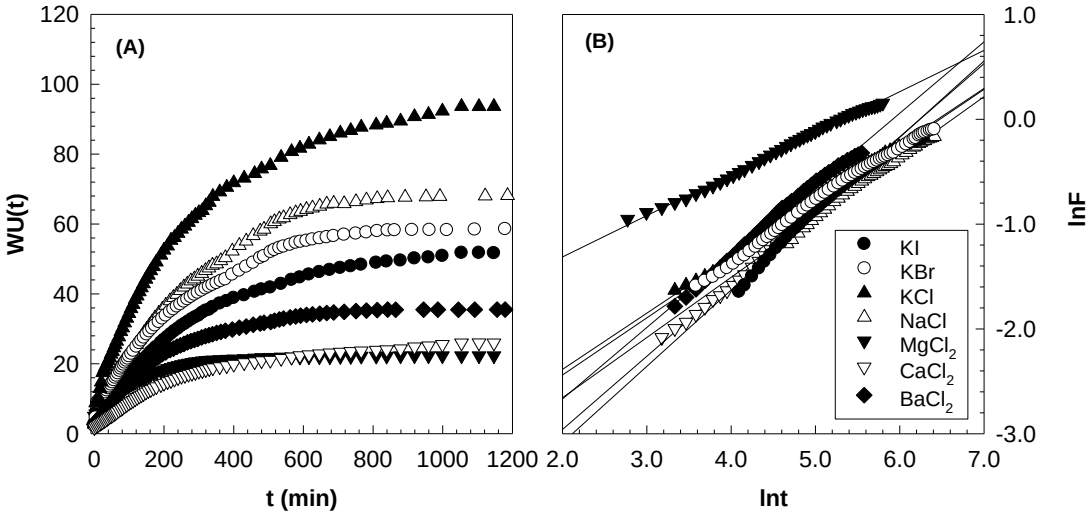

Figure 6.35 : Swelling dynamic curves of P(DMAEMA-co-HEMA) hydrogels containing 20 mol% HEMA in 1.0 M salt solutions as indicated (A) and ln–ln plots of *F* versus *t* (B).

For all studied systems an initial linear dependence of the fraction of water uptake of the gel, *WU(t)*, as a function of *t* is observed. The rapid initial mass increase of the hydrogels is governed by the diffusion of water from the external solution to the gel, induced by the difference of salt concentration inside the gel and in the external solution. Then, the swelling speed is reduced which can be connected with structural relaxation of the polymer chains of the network while complexes of the polymer network are formed. The process of formation of such complexes proceeds with a considerably smaller speed in comparison with water diffusion. Finally, a plateau region is observed when the equilibrium swelling is reached. The data from the kinetics of swelling in salt solutions for the copolymer hydrogels were analyzed by

Eq. (3.24) and Eq. (6.10) was applied to calculate the diffusion coefficient values of water moving through the P(DMAEMA-co-HEMA) hydrogels and the results were summarized in Table 6.7. The values of the exponent *n*, characteristic of the transport mode, were determined from ln*F* versus ln*t* plot in Fig 6.35(B). These values were already listed in Table 6.7, and obtained by regression for the seven salts.

Table 6.7 : Parameters for the kinetic swelling for the salt solutions: Initial diffusion coefficient *D* (cm^2/s), kinetic exponent *n* and characteristic constant *k* from fitting experimental data.

Saline Solution	***n***	**ln*k***	***k***	**r^2**	**D (cm^2/s)**
KI	0.7088	-4.449	0.0116	0.9884	1.02×10^{-6}
KBr	0.5449	-3.529	0.0293	0.9954	3.07×10^{-6}
KCl	0.5362	-3.458	0.0314	0.9944	3.37×10^{-7}
NaCl	0.5742	-3.804	0.0222	0.9943	3.13×10^{-7}
MgCl2	0.3934	-2.098	0.1226	0.9960	8.26×10^{-7}
CaCl2	0.6863	-4.305	0.0134	0.9963	1.13×10^{-6}
BaCl2	0.6813	-4.030	0.0177	0.9950	1.68×10^{-6}

The observation of the values of *n* between 0.68-0.70 for KI, $CaCl_2$ and $BaCl_2$ - neither 0.5, which would mean Fickian diffusion, nor 1, which would be case II- indicates non-Fickian behavior. These results indicate that the swelling transport mechanism was a non-Fickian type. For KBr, KCl and NaCl, *n* values between 0.53-0.57 indicates that the diffusion is Fickian or anomalous, but not “case II” type. For $MgCl_2$, *n* was below 0.5 which is regarded as Fickian diffusion, is named as "Less Fickian" behavior. pH-sensitive hydrogel composed of N[-3(dimethylamino)propyl] methacrylamide (DMAPMA) and 2-hydroxyethyl methacrylate (HEMA) was prepared by Mishra et al. using N,N-methylene bisacrylamide as crosslinker and sodium persulfate/ammonium persulfate as joint initiator system. It was observed that the calculated value of n for the gel at both physiological fluids is 0.79 and 0.87, respectively, which confirms the non-Fickian release mechanism [122].

The dynamic shrinking kinetics of P(DMAEMA-co-HEMA) hydrogels from the swollen state (in 10^{-5} M salt solution) to the shrunken state (in 1.0 M salt solution) were measured and the curves were collected in Figure 6.36. It can be seen that the shrinking of P(DMAEMA-co-HEMA) hydrogels in the presence of different salts depends on the specific interaction of the salt with the polymer chains. It was observed that in 1.0 M salt solutions, the swelling ratio of P(DMAEMA-co-HEMA)

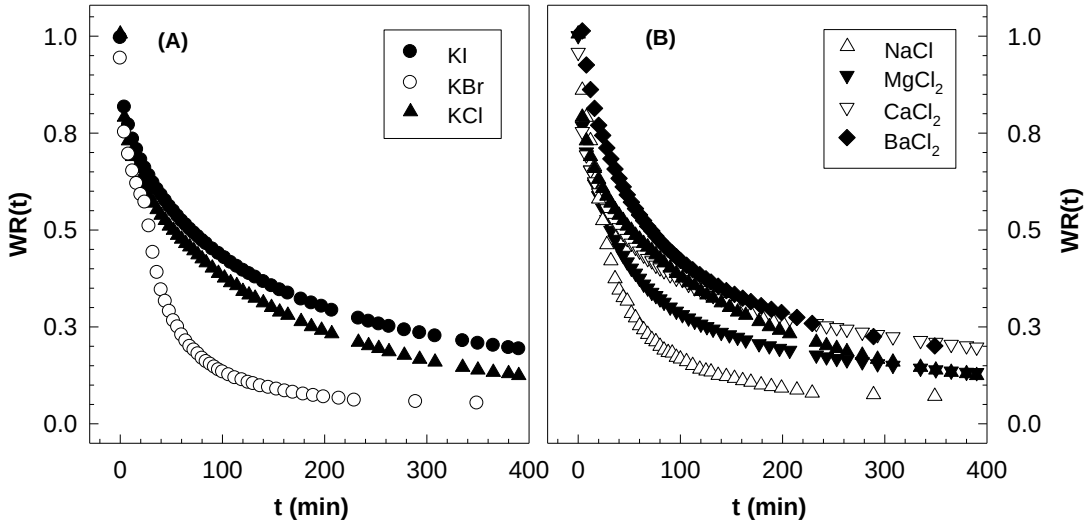

Figure 6.36 : Shrinking dynamic curves of P(DMAEMA-co-HEMA) hydrogels containing 20 mol% HEMA in 1.0 M salt solutions as indicated.

hydrogels decreases rapidly due to the difference between the mobile ion concentration inside and outside of hydrogel. However, the data illustrate that the initial collapse rate of hydrogels is differ from each other due to the specific interactions between salt and polymer chains. P(DMAEMA-co-HEMA) hydrogels in KBr and NaCl solutions shrank significantly faster than the other types of salt solutions. The equilibrium state of the gel collapse is reached in 6 h., while for the hydrogel samples in KBr and NaCl solutions, the processes are completed after ca. 3 h. For example, P(DMAEMA-co-HEMA) hydrogel sample had its water retention reduced from 100% to close 8.5% within 200 min in NaCl solution and to 7.4% in KBr solution, whereas it was reduced to only about 21.9 % in $BaCl_2$ solution within the same time frame. The initial shrinking kinetics is mainly determined by the difference of salt concentration inside and outside the gel and is unaffected by specific interactions, e. g., hydrophobic forces.

7. CONCLUSIONS AND RECOMMENDATIONS

The conclusions that can be drawn from the swelling and elasticity measurements of P(DMAEMA-co-HEMA) hydrogels can be summarized as follows:

i. The free-radical copolymerization of DMAEMA and HEMA in the presence of cross-linking agent DEGDMA results in cationic hydrogel networks with the extent of swelling controlled by changing the comonomer HEMA concentration and the temperature. The swelling behavior of P(DMAEMA-co-HEMA) hydrogels was investigated in water as a function of the comonomer HEMA content and the temperature. The effects of the HEMA content on the characteristic properties of P(DMAEMA-co-HEMA) hydrogels have been studied in comparison with that of homopolymeric PDMAEMA and PHEMA hydrogels.

It was observed that the hydrogels with higher DMAEMA content (100-70 mol-%) exhibit noticeable swelling ratios in water and are able to increase their volume 25-fold with respect to after-preparation state. In the case of DMAEMA rich comonomer hydrogels, the concentration of ionizable groups increased with increasing DMAEMA, which enhanced the extent of the swelling. It was found that increasing HEMA content of the copolymer caused a gradual decrease in the swelling ratio of the resulting hydrogels. The decrease in swelling with increasing HEMA content can be related with the formation of hydrophobic domains including pendant moieties belonging to different network subchains.

The effect of temperature on the swelling behavior of P(DMAEMA-co-HEMA) hydrogels in water was also investigated and a strong temperature dependence was accounted for the copolymeric hydrogels with higher DMAEMA content. The temperature increment leads to lower swelling values indicating that the temperature decrease favors the uptake of water into the hydrogel structure.

The uniaxial compression testing results at a state both after preparation and after equilibrium swelling in water showed that the incorporation of HEMA significantly enhanced the mechanical properties of P(DMAEMA-co-HEMA) hydrogels. As the content of HEMA increased, the elastic modulus and the effective crosslink density

of resulting hydrogels increased. It was found that the P(DMAEMA-co-HEMA) copolymeric hydrogels exhibit much higher toughness than that of the corresponding pure P(DMAEMA) hydrogel. P(DMAEMA-co-HEMA) copolymeric hydrogels having more elastic character and higher mechanical strength relative to homopolymeric PDMAEMA gel could be achieved by the proposed copolymerization procedure. The addition of 30 mol% HEMA into the PDMAEMA network structure results in ten-fold increasing in the elastic modulus when compared with the homopolymeric PDMAEMA hydrogels. The improvement in the mechanical properties can be attributed to the ability of the comonomer HEMA to reinforce the network structure of P(DMAEMA-co-HEMA).

The swelling behavior of P(DMAEMA-co-HEMA) copolymeric hydrogels in water was also analyzed by using Flory-Rehner theory of swelling equilibrium and the interaction parameters χ of the P(DMAEMA-co-HEMA) – water system were calculated at different temperatures. It was found that the interaction parameter χ of the P(DMAEMA-co-HEMA) – water system increase with increasing HEMA content which is expected due to increase in the interactions between hydrophobic groups of the polymer chains.

ii**.** In the second part of this thesis, the P(DMAEMA-co-HEMA) hydrogels were characterized in terms of the maximum swelling ratio, the dynamic swelling kinetics and the elasticity in buffer solutions of different pH. It was observed that the swelling ratio of P(DMAEMA-co-HEMA) copolymeric hydrogels is significantly affected as the pH of the swelling media and the composition of the copolymer network changes. The equilibrium swelling volume is a balance between the osmotic pressure of the protonated polymer network and the elasticity of the network. A discontinuous pH-dependent phase transition in the swelling ratio–pH curve was observed and it was shown that the cation rich copolymer swelled in acidic condition, and shrank in alkaline condition. It was found that the amount of DMAEMA incorporated into the network structure affects the degree of pH sensitivity due to the content of quaternizable tertiary amine groups.

The equilibrium and dynamic response against the temperature were also investigated for the gel matrices produced by changing the initial DMAEMA/HEMA content in the copolymerization feed. In all compositions, the maximum extent of swelling were obtained at the lowest pH of 2.1, this being due to complete

protonization of amino groups of DMAEMA at this pH value. It was observed that the degree of swelling of P(DMAEMA-co-HEMA) hydrogels decreases with increasing pH. Because positively charged tertiary amino groups are incorporated into the polymer network, the gel swells in the low pH region, due to the ionic repulsion of the protonated amino groups, and collapses in the high pH region, due to unprotonated amino groups. The results also indicated that an increase in the pH from 7.7 to 8.0 decreased the water uptake and the equilibrium swelling degree of hydrogels dramatically and hence, P(DMAEMA-co-HEMA) hydrogels showed pH-dependent volume transition behavior. This is due to the fact that as the alkalinity of the buffer solution increases, the concentration of ionized groups in the polymer decreased drastically.

In order to analyze dual pH- and temperature- sensitivity of P(DMAEMA-co-HEMA) copolymeric hydrogels, the swelling studies were also carried out at various temperatures for the whole range of composition. When the temperature is below 45^{o}C, the hydrogels are in the swollen state due to the binding water caused by the hydrogen-bonding force between the water and the polymer chains. Since the hydrogen-bonding force is reduced by increasing the temperature, the binding water turns to the free water which can be moved out of the polymeric network structure. This fact becomes more evident with increasing temperature. In fact, at temperatures above 45 ^{o}C, the extent of the pH-induced collapse transition decreases for the whole range of composition.

The effect of comonomer HEMA on the water content of copolymeric P(DMAEMA-co-HEMA) hydrogels was studied by monitoring the change of volume swelling as a function of the temperature. Increase in HEMA content in the network reduced swelling degree dramatically at all pH values, especially, when the concentration of HEMA was relatively high. pH-dependent volume transition of P(DMAEMA-co-HEMA) copolymer hydrogels disappears with increasing the HEMA content of the copolymer structure.

The elasticity of P(DMAEMA-co-HEMA) hydrogels was investigated under different pH conditions. The elastic modulus of hydrogels changes depending on the pH of the swelling medium. In acidic pH region, the elastic moduli of hydrogels increase slightly with increasing pH from 2.1 to 7.7. A sharp increase in the elastic moduli of hydrogels was also observed in a narrow range of pH between 7.7 and 8.0

which corresponds to the pH-dependent volume transition of P(DMAEMA-co-HEMA) copolymeric hydrogels. An increase in pH led to a decrease in the ionization of the network and reduced the swelling of the hydrogel, and hence to an increase in the modulus. It was also observed that the elastic modulus of P(DMAEMA-co-HEMA) hydrogels changes depending on the comonomer HEMA content used in the preparation. In a particular pH, increasing the HEMA content of the hydrogels increases the value of G. The addition of a small fraction of HEMA led to a significant increase in the effective crosslink density of P(DMAEMA-co-HEMA) hydrogels.

From the dynamic swelling-shrinking kinetic measurements of P(DMAEMA-co-HEMA) hydrogels, the diffusion coefficient of water within the gel matrix was estimated for swollen states by applying power law equation on the dynamic swelling behavior of gels prepared in the cylindrical form. The diffusion coefficients of P(DMAEMA-co-HEMA) hydrogels were found in the range of 2.15 - 4.16×10^{-6} cm^2/s, all falling well within that which is typical for solute diffusion coefficients (10^{-6}-10^{-7} cm^2 /s) in rubbery polymers. *D* values obtained for the hydrogels decreased with an increase of the HEMA content in the copolymeric. This is a fact that the incorporation of HEMA into DMAEMA gel would diminish water to penetrate into the gel and the penetration of water into the gel becomes more difficult. These results showed that the incorporation of HEMA into the PDMAEMA hydrogels provided significant advantages for the applications of dual pH- and thermo-responsive gels having higher mechanical strength relative to PDMAEMA hydrogels.

The diffusional exponent *n* for the copolymeric hydrogels in buffer solutions of pH 2.1 are found in the range of 0.32 - 0.57. For the hydrogels containing HEMA below 40 mol%, *n* values are found to be slightly over 0.50 and the diffusion of water into hydrogels was taken as a non-Fickian type (anomalous diffusion). If HEMA mol% increases from 50 to 80, *n* values range between 0.47 and 0.32 manifest that the diffusion behavior of water in these hydrogels follows the Less Fickian mechanism and the dominant physical mechanism controlling the water uptake of these copolymeric hydrogels is diffusion.

iii. In the last part of this thesis, the swelling equilibria of the copolymeric hydrogels was carried out in aqueous solutions of NaCl, KCl, KBr, KI, $CaCl_2$, $BaCl_2$ and $MgCl_2$ with different concentrations. The swelling ratio of P(DMAEMA-co-HEMA)

copolymeric hydrogels depends on the salt concentration, on the comonomer composition inside the hydrogel, and on the specific interaction of the salt with the gel polymer chains. The swelling measurements in all types of salt solutions showed that P(DMAEMA-co-HEMA) hydrogels exhibit strong salt-sensitive swelling behavior over the entire range of the comonomer HEMA concentrations. The swelling of P(DMAEMA-co-HEMA) hydrogels in saline solutions was distinctly decreased when compared to the values measured in deionized water. During the swelling of P(DMAEMA-co-HEMA) hydrogels in salt solutions, the mobile counterion concentration in the external solution is higher than that of in the gel phase, which results in an osmotic pressure that water molecules flow from the gel to the solution phase so that P(DMAEMA-co-HEMA) hydrogels deswell as observed. It was found that the extent of equilibrium gel volume increases with the counterion in the following sequence of Ca^{2+}, Ba^{2+}, Mg^{2+}, Na^{+}, and K^{+} at the same ionic strength.

To investigate the effect of salt on the elasticity of P(DMAEMA-co-HEMA) copolymeric hydrogels, the uniaxial compression measurements were also performed on hydrogel cylinders in equilibrium with salt solutions. The influence of different type of salts on the elasticity after equilibrium swelling indicated that the elastic modulus of P(DMAEMA-co-HEMA) hydrogels increases as the comonomer HEMA content in the feed increased. The elastic modulus of hydrogels also increases with increasing the ionic strength of the salt solution. When the salt solution is diluted, the ions may interact with the side groups of the chains and exhibit ion-bonding property. Therefore, the binding of ions to the P(DMAEMA-co-HEMA) network chains causes an external swelling of the hydrogels which results in decreasing of the elastic modulus. The effective crosslink density values ν_e of hydrogels first increase with increasing salt concentration up to 10^{-3} M and then decrease with further increasing salt concentration.

The swelling-shrinking kinetics of P(DMAEMA-co-HEMA) hydrogels was also investigated in salt solutions. Further analysis of the swelling characteristics and water diffusion in the hydrogels synthesized under various conditions, showed that the structure of the hydrogels, the type of the salt used in the swelling is the main factor affecting the diffusion coefficient *D* and transport mechanism. The dynamic kinetic studies also demonstrated the importance of the salt concentration and indicated that the composition of the comonomers had significant influence on the

swelling behavior of the resulting gels. The initial shrinking kinetics is mainly determined by the difference of salt concentration inside and outside the gel. The observation of the values of *n* between 0.68-0.70 for KI, $CaCl_2$ and $BaCl_2$ indicated that the swelling transport mechanism was a non-Fickian type. For KBr, KCl and NaCl, *n* values between 0.53-0.57 indicates that the diffusion is Fickian or anomalous, but not "case II" type.

The results presented in this thesis provide valuable sets of the swelling and elasticity data in acrylate-based copolymeric hydrogel systems, especially for DMAEMA and HEMA copolymer systems that are relatively new from a diffusion point of view. Also, the synthesis protocol used in this work provides valuable tools to examine the enhanced mechanical properties of acrylate-based copolymeric hydrogel systems. The results in this thesis showed that the PDMAEMA gel strength can be improved by adjusting the crosslink density using appropriate amount of the comonomer HEMA in the preparation. It can be concluded that the concentration of DMAEMA, temperature, pH and the copolymer composition are the important factors affected on the characteristic features of the swelling and the volume transition behavior of P(DMAEMA-co-HEMA) copolymeric hydrogels. Obtaining these parameters for P(DMAEMA-co-HEMA) hydrogels indicates to what extent these systems are compatible with the desired degree of swelling. In future work, the physico-mechanical properties of copolymeric P(DMAEMA-co-HEMA) hydrogels can be adjusted to a significant degree by modulating the synthesis procedure, adding pore-forming agent or copolymerizing hydrophobic acrylate-based comonomers.

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APPENDICES

APPENDIX A:

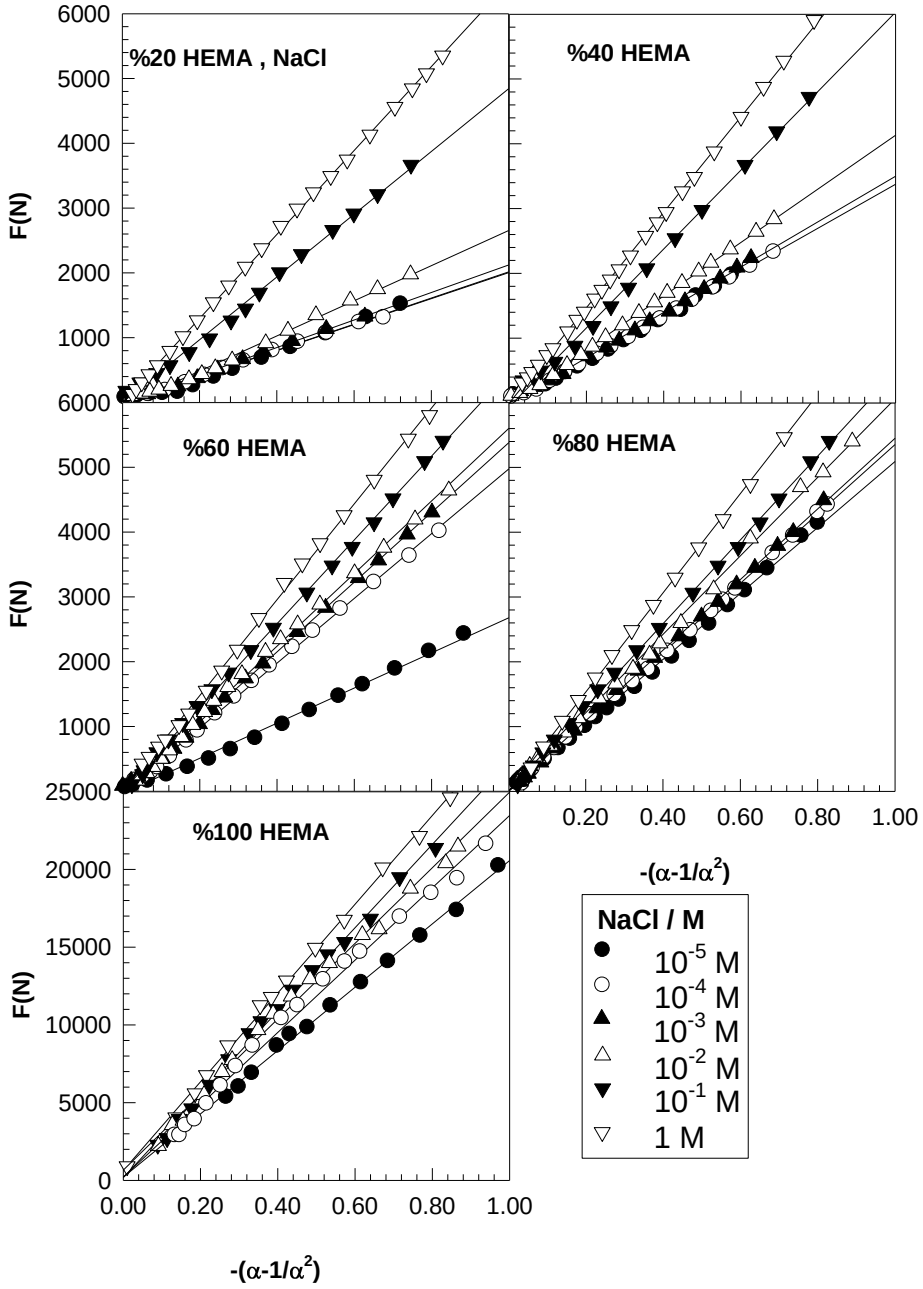

Figure A.1. Typical stress - strain data for P(DMAEMA-co-HEMA) hydrogels obtained from the compression tests after equilibrium swelling in NaCl solutions. The comonomer HEMA content and the ionic strength of the solutions are already indicated in the figure.

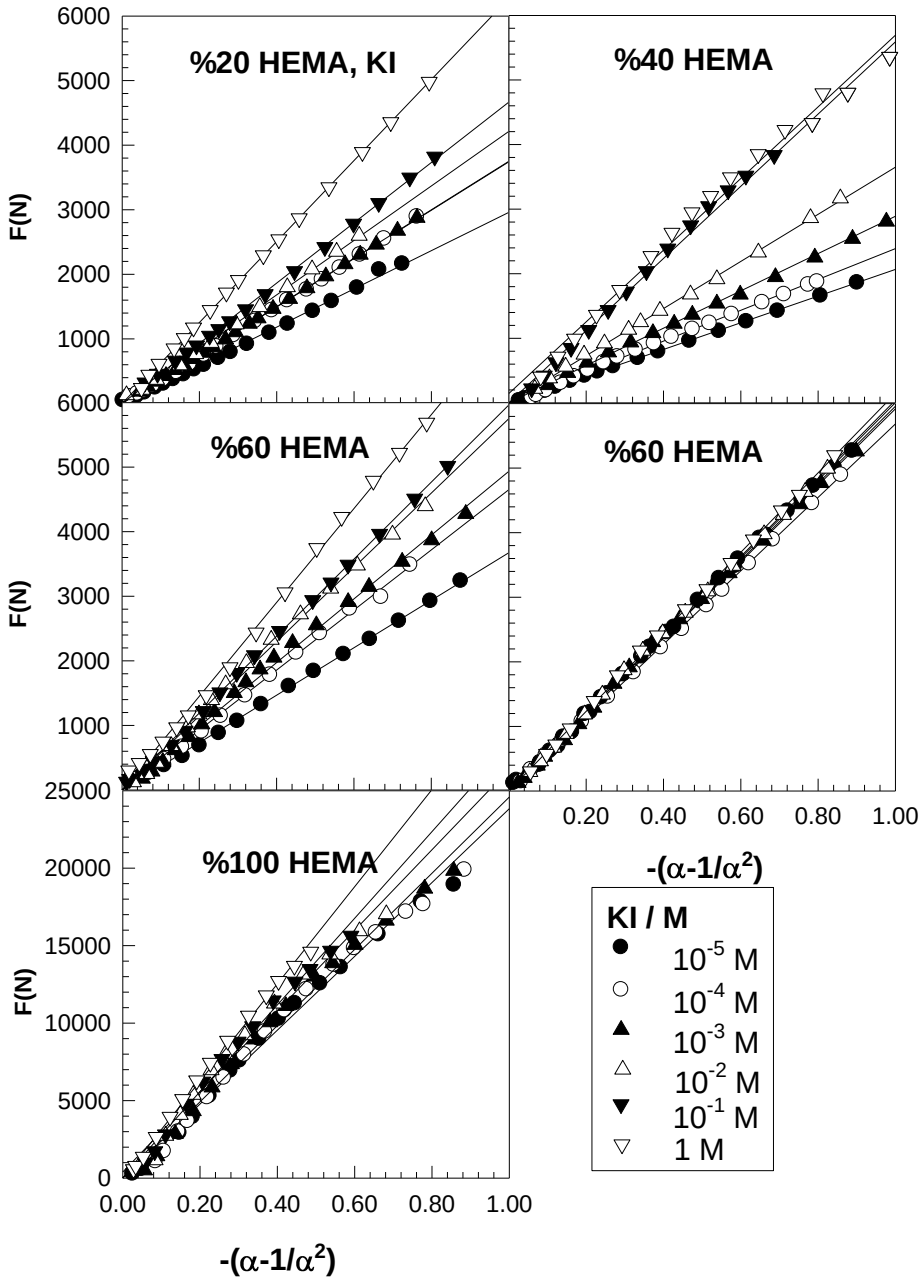

Figure A.2. Typical stress - strain data for P(DMAEMA-co-HEMA) hydrogels obtained from the compression tests after equilibrium swelling in KI solutions. The comonomer HEMA content and the ionic strength of the solutions are already indicated in the figure.

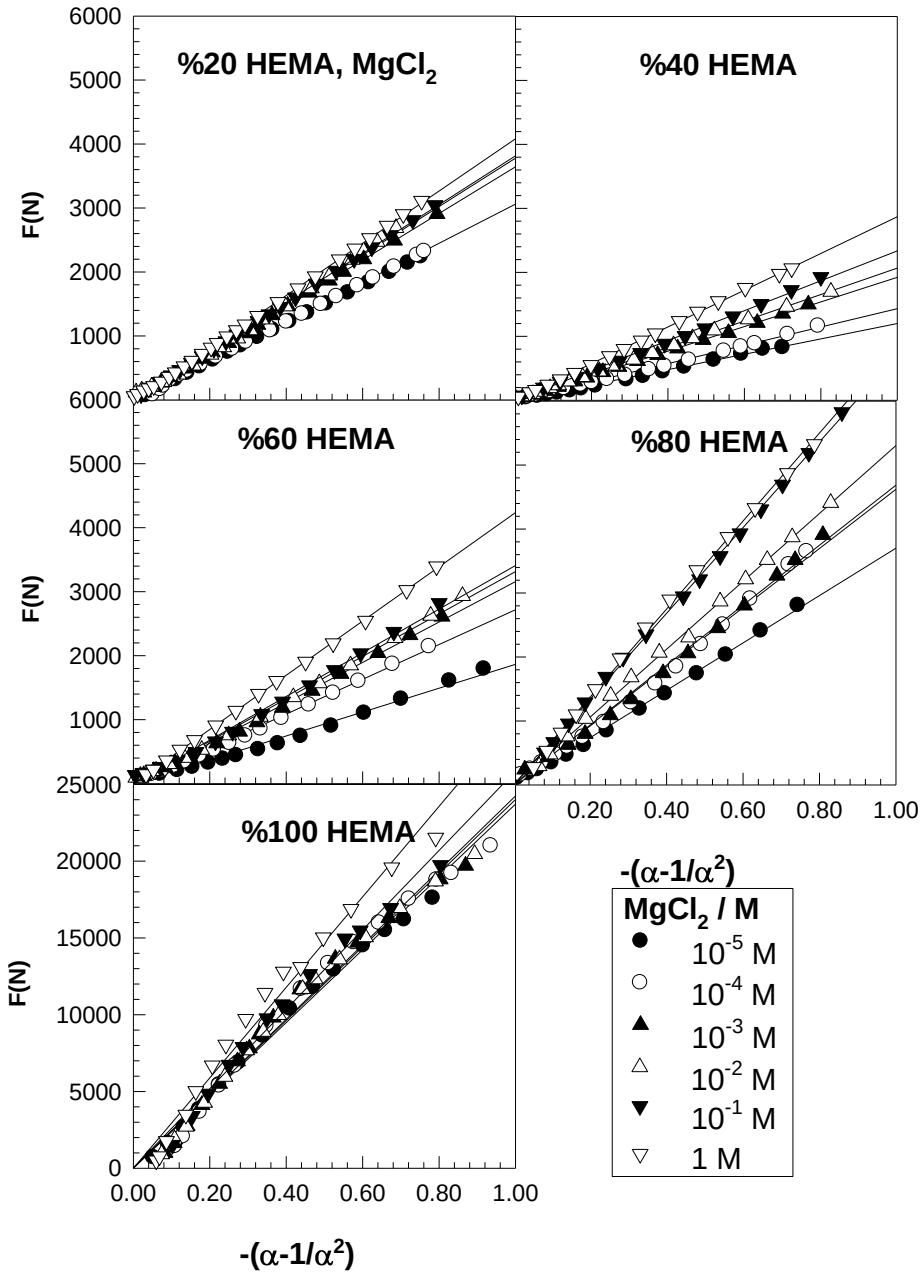

Figure A.3. Typical stress - strain data for P(DMAEMA-co-HEMA) hydrogels obtained from the compression tests after equilibrium swelling in $MgCl_2$solutions. The comonomer HEMA content and the ionic strength of the solutions are already indicated in the figure.

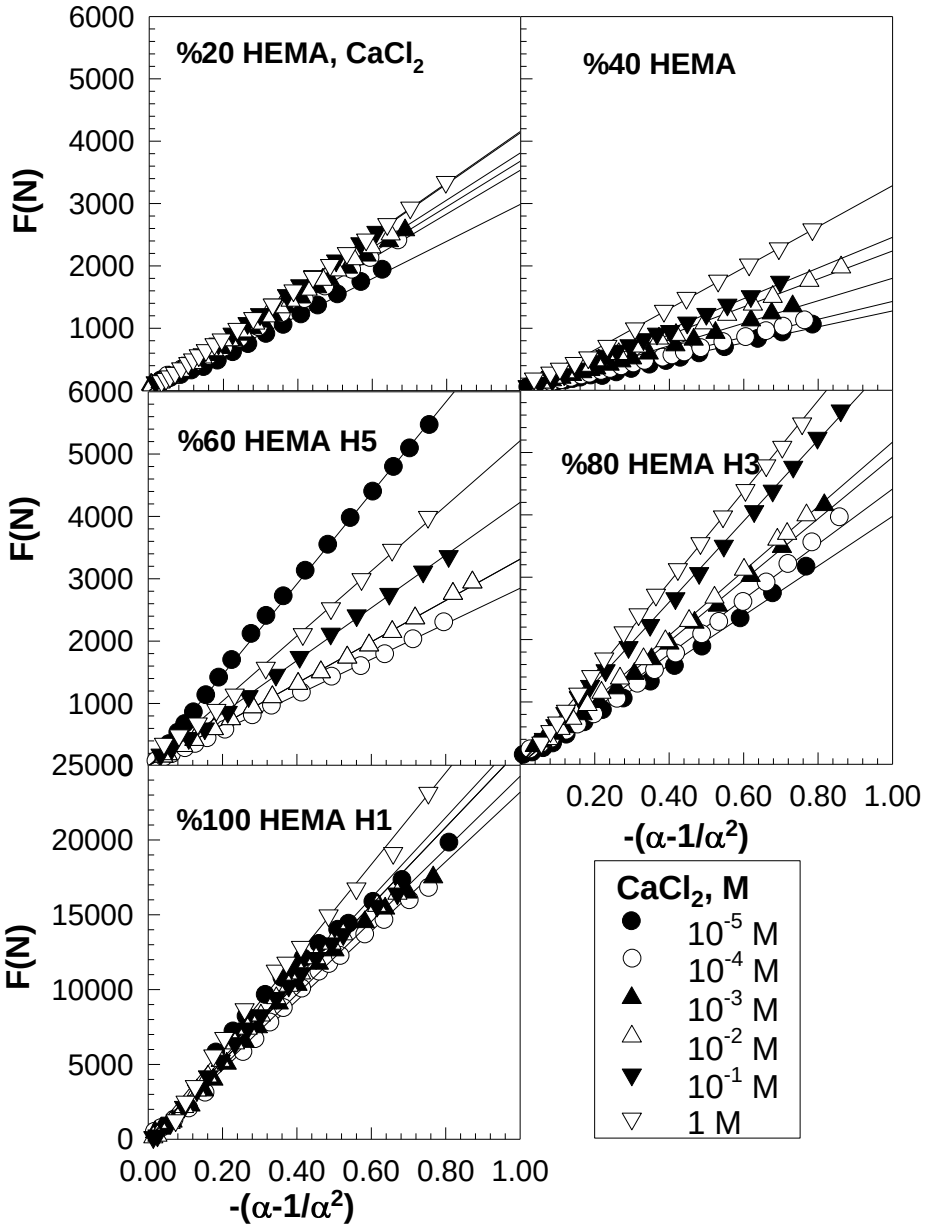

Figure A.4. Typical stress - strain data for P(DMAEMA-co-HEMA) hydrogels obtained from the compression tests after equilibrium swelling in $CaCl_2$ solutions. The comonomer HEMA content and the ionic strength of the solutions are already indicated in the figure.

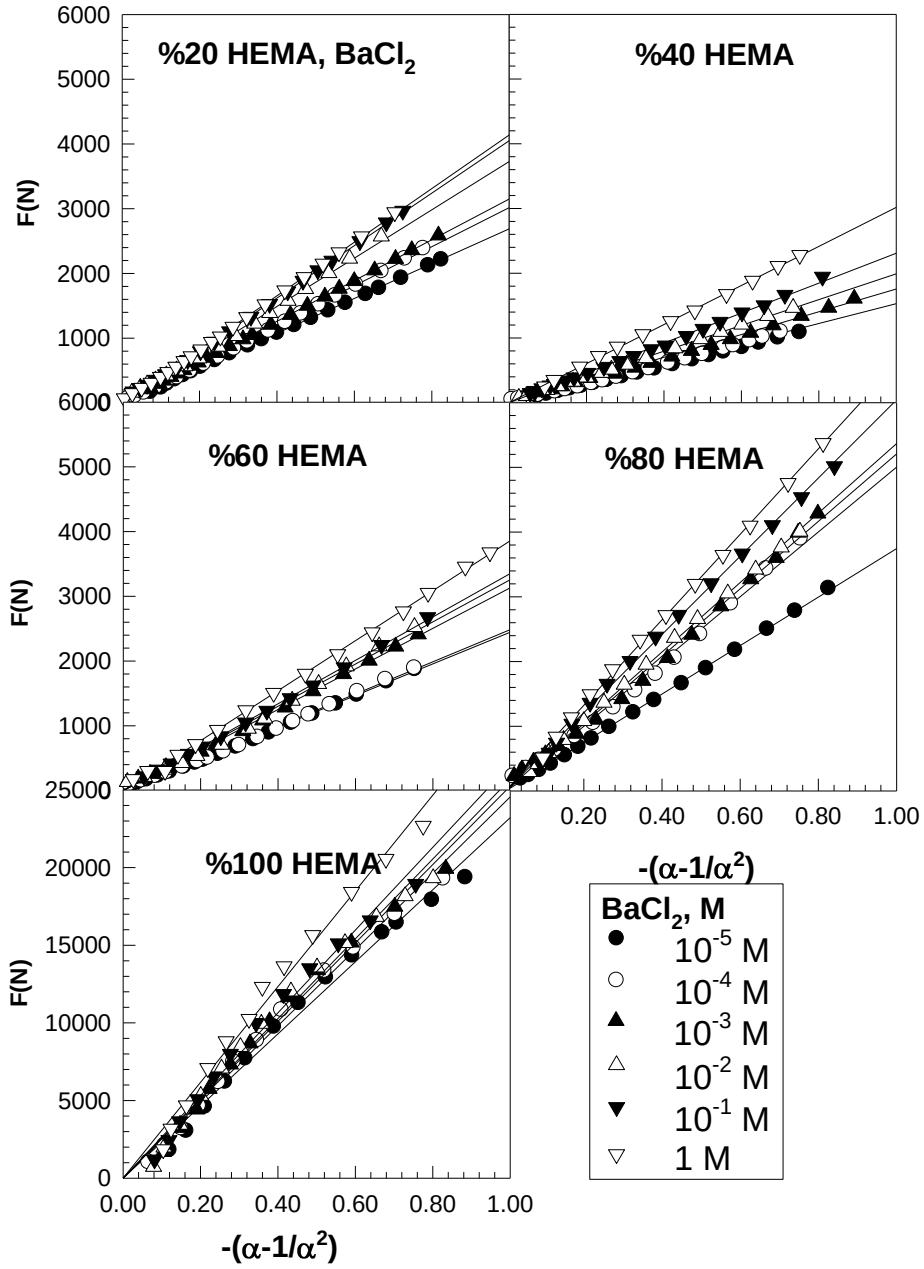

Figure A.5. Typical stress - strain data for P(DMAEMA-co-HEMA) hydrogels obtained from the compression tests after equilibrium swelling in $BaCl_2$ solutions. The comonomer HEMA content and the ionic strength of the solutions are already indicated in the figure.

CURRICULUM VITAE

Name Surname: Tayyibe ÇELİK

Place and Date of Birth: Istanbul, 04.10.1989

E-Mail: tayyibecelik@gmail.com

EDUCATION:

B.Sc.: Istanbul Technical University, Department of Chemistry, 2012

PUBLICATIONS:

- **Celik T, Orakdogen N.** "Effect of charge density on water sorption and elasticity of stimuli-responsive poly(acrylamide-itaconic acid) and poly(*N*,*N*-dimethylacrylamide-itaconic acid) hydrogels: Comparison of experiment with theory ." *Journal of Materials Research*, **2013**, 28, 3234-3244

PRESENTATIONS:

Celik T., Orakdogen N., 2014*:* Study of Cationic Poly(N,N-dimethylaminoethyl methacrylate) Hydrogels as pH-responsive Smart Materials. 2nd International Conference on Bio-Based Polymers and Composites, August 24-26, 2014, Visegrad, Hungary