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FABRICATION AND CHARACTERIZATION OF PH-RESPONSIVE POLY(ETHYLENE GLYCOL) METHYL ETHER METHACRYLATES – POLY(ACRYLIC ACID) HYDROGEL

By

SYAHIRA AMIRA BINTI MOHD SALLEH

Supervisor: Dr. Zuratul Ain Abdul Hamid

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DECLARATION

I hereby declare that I have conducted, completed the research work and written the dissertation entitled "**Fabrication and Characterization of pH Responsive Poly(ethylene glycol) Methyl Ether Methacrylates – Poly(acrylic acid) Hydrogel**". I also declare that it has not been previously submitted for the award of any degree or diploma or other similar title of this for any other examining body or university.

Name of Student : Syahira Amira Binti Mohd Salleh Signature:

Date : 3 July 2017

Witness by

Supervisor : Dr Zuratul Ain Abdul Hamid Signature:

Date : 3 July 2017

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LIST OF ABBREVIATIONS

AA	Acrylic Acid
ADA	Adenosine Deaminase
APS	Ammonim Persulfate
CST	Critical Solution Temperature
DN	Double Network
FDA	Food and Drug Administration
FTIR	Fourier Transform Infrared
IPN	Interpenetrating Polymeric Network
LCST	Lower Critical Solution Temperature
MBAA	N,N'-methylenebisacrylamide
MW	Molecular Weight
N_2	Nitrogen Gas
NaOH	Sodium Hydroxide
PAA	Poly(acrylic acid)
PEG	Poly(ethylene glycol)
PEGMA	Poly(ethylene glycol) Ethyl Ether Methacrylates
PEO	Poly(etheleneoxide)
PMMA	Ploy(methacrylic acid)
PVP	Poly(vinylpyrrolidone)
semiIPN	Semi Interpenetrating Polymer Network
seqIPN	Sequential Interpenetrating Polymer Network

LIST OF SYMBOLS

Q	Swelling ratio
W_f	Mass of hydrogel when fully swollen
W_d	Mass of hydrogel after drying

FABRIKASI DAN PENCIRIAN PH RESPONSIF POLY(ETILENA GLIKOL) METHYL ETHER METACRYLATES – POLY(ACRYLIC ACID) HIDROGEL

ABSTRAK

pH ionik responsif polimer mengandungi kumpulan asid (karboksilik atau sulphonik) atau kumpulan asas (garam ammonium) di mana bertindakbalas kepada perubahan pH dalam persekitaran biologi. pH responsif poli(etilena glikol)/poli(asid akrilik) (PEG/PAA) hidrogel disediakan dengan menggunakan pempolimeran radikal bebas dengan dua langkah proses pembentukan rangkaian berjujukan. Sampel disediakan ialah rangkaian tunggal PEG, PAA dan hibrid PEG/PAA hidrogel. Hidrogel kemudian diuji untuk menentukan sifat kimia dan sifat mekanik serta keupayaan responsif hidrogel terhadap pH pada pH larutan yang berbeza. Spektrometer Infra-Merah (FTIR) menunjukkan bahawa hidrogel PEG/PAA yang disintesis telah berjaya dicapai dengan kehadiran C-O-C regangan puncak getaran. Ujian mampatan telah digunakan untuk mengkaji kekuatan mekanik PEG, PAA dan PEG/PAA hidrogel. Keputusan ujian mekanikal menunjukkan bahawa kekuatan mekanik PEG/PAA hidrogel adalah lebih tinggi daripada rangkaian polimer tunggal. Di samping itu, tingkahlaku pH responsif juga dikaji dan keputusan mendapati bahawa nisbah pembengkakkan meningkat dengan pH yang semakin meningkat. Hasil dari kinetik bengkak/tidak-bengkak pada pH 3 dan pH 7 menunjukkan bengkak/tidak-bengkak kebolehbalikan berbanding daripada kinetik bengkak/tidak-bengkak pada pH 10 dan pH 7.

FABRICATION AND CHARACTERIZATION OF PH-RESPONSIVE POLY(ETHYLENE GLYCOL) METHYL ETHER METHACRYLATES – POLY(ACRYLIC ACID) HYDROGEL

ABSTRACT

The ionic pH sensitive polymer contains acid groups (carboxylic or sulphonic) or basic groups (ammonium salts) in which response to pH changes in the biological environment. The pH responsive poly(ethylene glycol)/poly(acrylic acid) (PEG/PAA) hydrogel was prepared by using free radical polymerization with a two-step sequential network formation process. The sample prepared are single network of PEG, PAA and hybrid of PEG/PAA hydrogels. The hydrogels were characterized to determine the chemical and mechanical properties as well as the responsive ability of hydrogels towards pH at different pH solution. The Fourier Transform Infrared (FTIR) Spectra showed that PEG/PAA hydrogels synthesized was successfully achieved as C-O-C stretching vibration peak was present. Compression test was used to study the mechanical strength of PEG, PAA and PEG/PAA hydrogels. The mechanical test results showed that the mechanical strength of PEG/PAA hydrogel were considerably greater than the individual polymer network. In addition, the pH responsive behaviour were also studied and it was found that the swelling ratio was increased with the increasing of pH. The result from swelling-deswelling kinetics at pH 3 and pH 7 showed good swelling/deswelling reversibility compared than swelling-deswelling kinetics at pH 10 and pH 7.

CHAPTER 1

INTRODUCTION

1.1 Background

Biomaterial are defined as any substance or combination of substances of synthetic or natural origin that can be used for any period of time, as whole or as part of a system which treats, augments, or replaces any tissue, organ or function of the body without causing local adverse reaction or systemic toxicity. Biomaterial should be either implanted for long or short term application, or used externally (Wong and Bronzino, 2007).

Novel synthetic technique have been developed in the last few years to impart desirable chemical, physical and biological properties to biomaterials. Materials have either been synthesized directly to obtain desirable chain segments or functional groups are built into the material, or indirectly, to add desirable segments or functional groups by chemical modification of existing structures. Modern biomaterials could be composed of various components, such as, metals, ceramics, natural tissues and polymer (Bae and Kim, 1998).

Polymeric materials have developed significantly over the past few decades. This material have high value application in technology and day-to-day life (Kunzier, 2003). The main advantages of polymeric biomaterials are ease of manufacturability to produce various shapes, ease of secondary process ability, reasonable cost and availability with desired mechanical and physical properties.

Polymers have gained importance in the pharmaceutical industry as both vehicles of drug carriage and drug encapsulates. Hydrogels are comprised of cross-linked polymer networks that have a high number of hydrophilic groups or domains.

Hydrogels are a special class of polymers that imbibe a considerable amount of water while maintaining their overall shape (Gupta et al., 2002).

The area of hydrogel research has expanded dramatically in the last decade, primarily because of hydrogels perform well in biomedical application (Gil and Hudson, 2004). Due to their ability to mimic the natural structure of the body's cellular makeup, hydrogels work well in the body. Their unique structure and properties also make hydrogels widely used in non-biomedical application (Das et al., 2006).

In comparison to other synthetic biomaterials, hydrogels resemble living tissues closely in the physical properties because of their relatively high water content and soft and rubbery consistency. Because of their low interfacial tension, hydrogels show minimal tendency to adsorb proteins from body fluids. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration.

Hydrogels have been coined as 'intelligent gels' or 'smart hydrogels' because of its ability to receive, transmit or process a stimulus, and respond by producing a useful effect. Hydrogels are 'smart' or 'intelligent' in the sense that that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behaviour, resulting in the release of entrapped drug in a controlled manner. Most of the time, drug release is observed during the swelling of the hydrogel (Gupta et al., 2002).

1.2 Problem Statement

The hydrogel is one class of polymers that comprised of three-dimensional network structures that have a unique capability as a non-soluble, highly swollen material. (Gong et al., 2001). Responsive hydrogels can swell or shrink depending on external applied triggers such as temperature, pH and solvent composition of the

coexisting phase, electric fields, light, etc. The volume change of pH sensitive hydrogel gives interest for controlled drug delivery area. pH-sensitive hydrogels contain weak anionic and/or cationic comonomers (Ninni et al., 2013). Despite their high potential as smart materials, their low mechanical strength is a significant disadvantage for some applications

Poly(ethylene glycol) (PEG) is a biocompatible, non-toxic, non-immunogenic and water soluble polymer which widely used in biomaterial, biotechnology, and medicine. PEG derivatives were used in covalent attachment to protein to reduce immunogenicity, proteolysis and kidney clearance and to enhance solubility. PEG derivatives have also been employed in the drug delivery field. Although macromolecular networks with PEG as a polymeric component have been largely synthesized, however, they have an obvious limitation manifested in the low swelling of the hydrogel forms. Whereas, poly(acrylic acid) (PAA) has a great number of ionizable acid groups which is carboxylic acid. The carboxylic groups accept protons at low pH values and release protons at high pH values. So when the pH increases, the polymer swells due to the electrostatic repulsion of the negatively charged group (Bajpai et al., 2001).

To address both limitations, synthesis of PEG and AA via free radical polymerization is proposed. The resulted hydrogel expected to have a higher swelling ratio and good mechanical properties than the individual polymer network. Besides, drug enclosed within a hydrogel were able to swell and deswell responding to change in pH.

In this research, the PEG and AA were chemically synthesized using ammonium persulfate (APS) as initiator and N,N'-methylenebisacrylamide (MBAA) as crosslinking agent via free radical polymerization. When pH sensitive polymeric chains are crosslinked forming hydrogels, their behaviour is influenced by the nature of the ionisable groups, the polymer composition, and the hydrophobicity of the polymer backbone, but also by the crosslinking density (Aguilar et al., 2007). PEG chain lengths with higher

molecular weight exhibited the significantly higher strength. Adjusting the amount of carboxylic acid groups in hydrogel system gave a good site of drug release at specific pH value (Liu et al., 2017).

1.3 Research Objectives

1. To study the effect of different molecular weight of poly(ethylene glycol) methyl ether methacrylates (PEGMA) oligomonomers on pH responsive hydrogels properties
2. To study the effect of acrylic acid (AA) loading on pH responsive hydrogels properties
3. To study the effect of different pH solution on pH responsive hydrogels properties

1.4 Thesis Outline

Chapter 1 discussed the background of hydrogel, the problem statement and the objective of this research

Chapter 2 reviews the scientific literature on hydrogel structure and the classification of hydrogels. In addition, different preparation methods of hydrogels were examined to see which may be successful to improve the mechanical properties of the hydrogel materials. Next, the significance of the hydrogels in drug release and tissue engineering application and the background of materials used for the synthesis of the hydrogels.

Chapter 3 describe the experimental method used to prepare the single pH responsive network and double pH responsive network hydrogel in this study. This begins with synthesis procedures for the first network hydrogel (PEGMA), second network hydrogel (PAA) and hybrid PEG/PAA network of pH responsive hydrogels. This chapter also describe the characterization technique used.

Chapter 4 discussed the actual characterization results which then used to understand and interpret the behaviour of the swollen single and double network of pH responsive hydrogels.

Chapter 5 presents concluding remarks and makes suggestions for future direction in which the work in this study can be expanded.

CHAPTER 2

LITERATURE REVIEW

2.1 Hydrogels

Hydrogels are hydrophilic polymer chains cross-linked to form an interconnected network resulting in an insoluble gel. Due to their cross-linked structure, hydrogels can absorb several hundred up to one thousand times their dry weight in water giving them solid-like properties. This means hydrogels have a defined shape and mechanical properties. However, hydrogels also exhibit liquid-like properties such as the ability of solute molecules to diffuse through matrix. The properties of a hydrogel can be manipulated in a variety of ways (Lee et al., 2004).

Hydrogels usually composed of three-dimensional polymer network structure and large amount of water (50-90%) inside the network structure and have potential applications in many fields. Beside their wide variety of applicability such as drug delivery system, superabsorbent, microfluidics, and contact lenses in the materials science domain, they have become extensively attractive in tissue engineering because of their stimuli responsive property. However, most of synthetic hydrogel suffered from a lack of mechanical strength compares with the hydrogel-like bio-tissues (Haque et al., 2012).

Hydrogels can retain a large amount of water without dissolving their structure, and due to their properties they are similar to living tissues. However, conventional hydrogels composed of one single network are generally brittle and can break easily after application of little force. In order to overcome this problem, an interesting strategy could be the formation of an interpenetrating polymeric network (IPN) with improved properties that are often considerably different from those the macromolecular constituents (Pacelli et al., 2014). Approaches have been taken to enhance the

mechanical properties, among which IPN structure comprising a synthetic monomer and a hydrocolloid have found to be the most effective. This results to an aqueous monomer solution containing an iono-gelling hydrocolloid is polymerized in the presence of a chemical crosslinker and treated with salts afterwards. Salts help to change the semi-IPN structure of the hydrogel to a full IPN hydrogel with enhanced wet strength (Omidian and Park, 2012)

As these three-dimensional hydrophilic networks being insoluble, it can retain a large amount of water which contributes to their good blood compatibility and maintains a certain degree of structural integrity and elasticity. –OH, -COOH, -$CONH_2$ and –SO_3H which are types of hydrophilic functional groups present in the hydrogel that capable of absorbing water without undergoing dissolution.

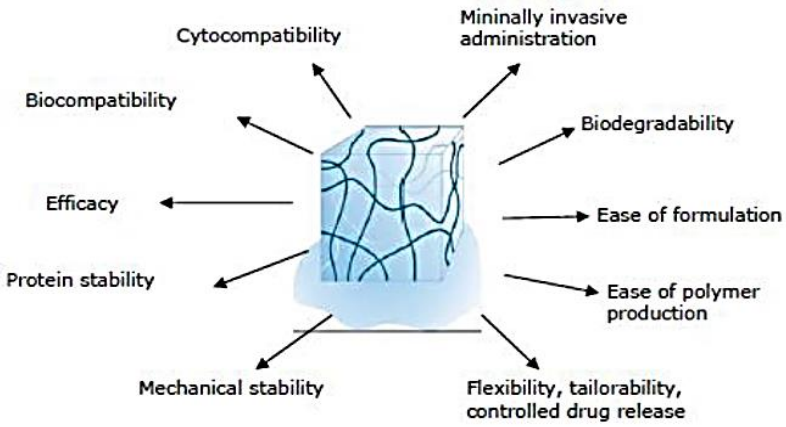

Figure 2.1: Overview of the ideal characteristics of a hydrogel for biomedical and pharmaceutical applications (Omidian and Park, 2012)

Hydrogels are three-dimensional polymeric network capable of absorbing large amount of water while maintaining their structural stability. Hydrogel can imbibe a water content up to 99 % of its dry weight, and swell greater than 10 times in volume, without dissolution (Ionov, 2014). Hydrogels are soft, pliable materials which often exhibit

excellent biocampability due to their high water content and unique swelling properties. Thus, possess many biological traits resembling natural living tissue both compositionally and mechanically (Sirousazar and Kokabi, 2012). Throughout the past few decades, application of these impressive materials has rapidly expanded to areas including sensing, drug delivery, tissue engineering and regenerating medicine.

During immersion into an aqueous environment, the polymer network will imbibe water until it reaches a swollen equilibrium state, whereby the osmotic force solvating the repeating units of the macromolecular chains is counter-balanced by the elastic force of the cross-linked structure. In retaining the three-dimensional integrity of the swollen polymer network, it is important to have chemical or physical crosslinks in the network structure. In chemically cross-linked hydrogels, crosslinking agents are utilised to covalently bind the polymer chains. Once formed, these gels possess permanent properties such as shape, size etc. and are no longer soluble. Whereas, in physically cross-linked hydrogels, polymer chains are held together via non-covalent interactions such as hydrogen bonding, hydrophobic interactions, van der Waals forces, chain entanglements and ionic interactions. Thus, these hydrogels can undergo conformational changes and possess sol-gel reversibility (Omidian and Park, 2012). This means that these polymers can display liquid or solid behaviour depending on environmental conditions.

Synthesis of chemically cross-linked hydrogels is primarily based upon the reaction of hydrophilic monomers, initiators and crosslinkers. Common methods of preparation involve copolymerisation or free radical polymerisation using monomers such as polyethylene glycol, acrylic acid and methacrylic acid. Water as aqueous solutions, are used as diluents to control the heat of polymerisation and the final hydrogel properties (Ahmed, 2013). The connecting of the macromolecular chains together to form a progressively larger branched polymer is referred to as gelation and the ‘gel point’ is the first appearance of this structure. The important factors in determining the overall

properties of the hydrogel are choice of monomer, cross-linker, ratio of monomer to cross-linker, reaction time and reaction temperature. These factors are selected carefully to tailor gels for specialised applications (Ottenbrite et al., 2010).

2.1.1 Physical and Chemical Hydrogels

In physical hydrogels, the nature of the crosslinking process is physical which normally achieved via utilizing physical processes such as association, aggregation, crystallization, complexation and hydrogen bonding. A chemical process such as chemical covalent crosslinking is utilized to prepare a chemical bonding. Figure 2.2 and Figure 2.3 show different approaches to make physical and chemical hydrogels, respectively. Physical hydrogels are reversible due to the conformational changes, whereas, chemical hydrogels are permanent and irreversible as a result of configurational changes (Omidian and Park, 2012).

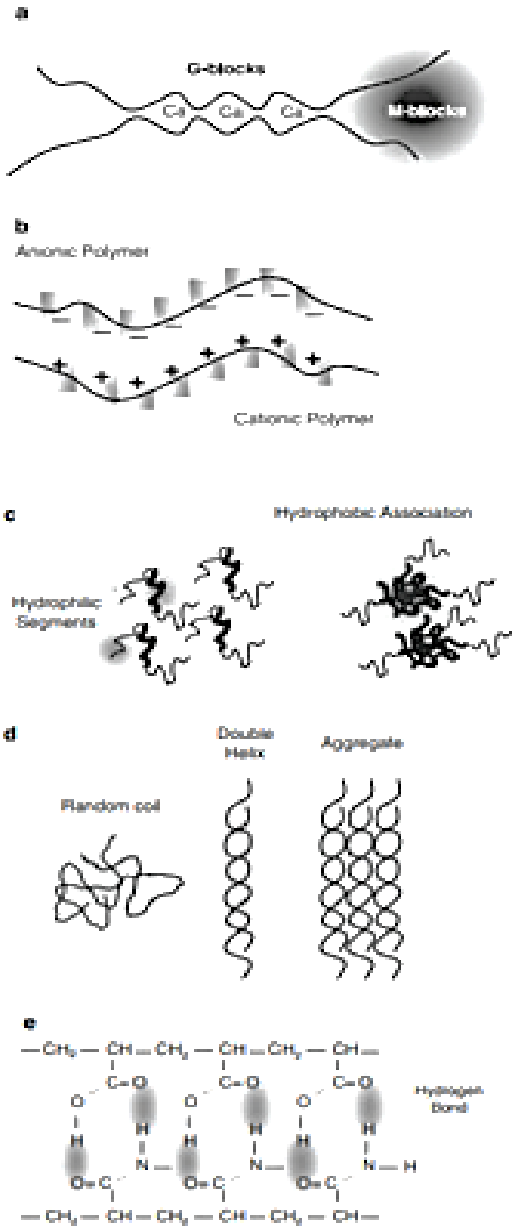

Figure 2.2: Example of physical hydrogels crosslinked by (a) ion-polymer complexation, (b) polymer-polymer complexation, (c) hydrophobic association, (d) chain aggregation and (d) hydrogen bonding (Omidian and Park, 2012)

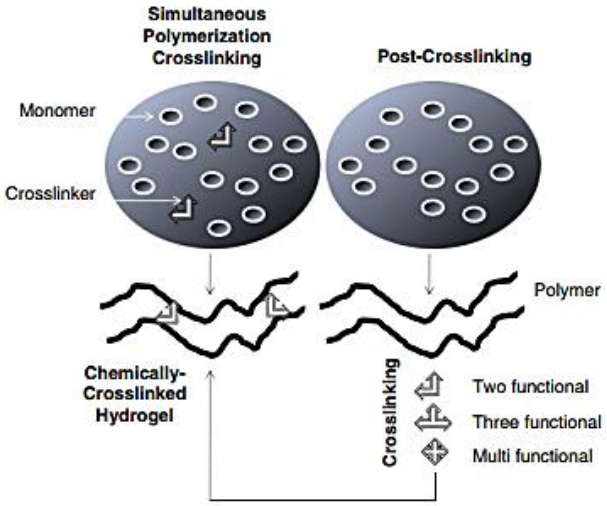

Figure 2.3: Methods to prepare chemical hydrogels (Omidian and Park, 2012)

2.2 Classifications of Hydrogels

Hydrogels can be classified as neutral or ionic based on the nature of side groups. The driving force for swelling in neutral hydrogels is due to the water-polymer thermodynamic mixing contribution to the overall free energy, along with elastic polymer contribution (Peppas et al, 2000). The ionic interactions between charged polymers and free ions can contributed to the swelling of ionic hydrogels (Peppas and Khare, 1993). Poly (acrylic acid) and polyamines which are ionic hydrogels, contains ionic groups such as carboxylic acid that imbibe larger amount of water, because of its increased hydrophilicity. Hydrogels can also be classified as homopolymers or copolymers depending on the method of preparation. Hydrogels can be classifies based on the physical structure of the network as hydrogen bonded structures, super molecular structures, hydro colloidal aggregates, amorphous and semi-crystalline (Peppas et al., 2000). The stimuli responsive gels are important classes of hydrogels (Ji et al, 2006). They show swelling behaviour dependent on their physical environment. These gels can swell, or de-swell in response to changes in pH, temperature, ionic strength, and electromagnetic radiation (George and Abraham, 2007). Thus can be used in application

such as separation membranes, biosensors, artificial muscles and drug delivery devices (Lin and Metters, 2006).

2.2.1 Stimuli Responsive Hydrogels

Hydrogels have been developed as stimuli-responsive materials that undergo abrupt volume change in response to small changes in biological environmental parameters such as temperature, pH, ionic strength, etc. Due to these unique characteristics of hydrogels, it give a great interest in drug delivery, cell encapsulation and tissue engineering (Plunkett et al., 2005). Stimuli-responsive is important in the development of novel smart hydrogels (Zhang, 2001).

The most important systems from a biomedical point of view are those sensitive to temperature and/or pH of surroundings. The human body exhibits variations of pH along the gastrointestinal tract, and also in some specific areas like certain tissues and subcellular compartment (Abbaszadeh et al., 2014). An abrupt readjustment in small ranges of pH or temperature due to polymer-polymer and polymer-solvent interactions. As for pH sensitive polymers, the key element of the system is the presence of ionisable weak acidic or basic moieties attached to a hydrophobic backbone. The coiled chains extend dramatically, responding to the electrostatic repulsions of the generated charges (anions or cations) upon ionization (Aguilar et al., 2007).

Stimuli responsive hydrogels have found a lot of applications in biomedical and pharmaceutical fields, where they are used for reconstruction of cartilages, artificial tendons and organs, soft contact lens, and self-regulated, pulsatile or oscillating drug delivery systems. Furthermore, they also found application in medicine for making chemical valves, immobilization of enzymes and cells, concentrating dilute solutions in bioseparation, and in bulk engineering for microfluid devices, motors/actuators, and sensors.

Stimuli-responsive or smart-gels is gels that exhibiting a phase transition in response to change in external conditions such as pH, ionic strength, temperature and electric currents (Tiwari et al, 2012).

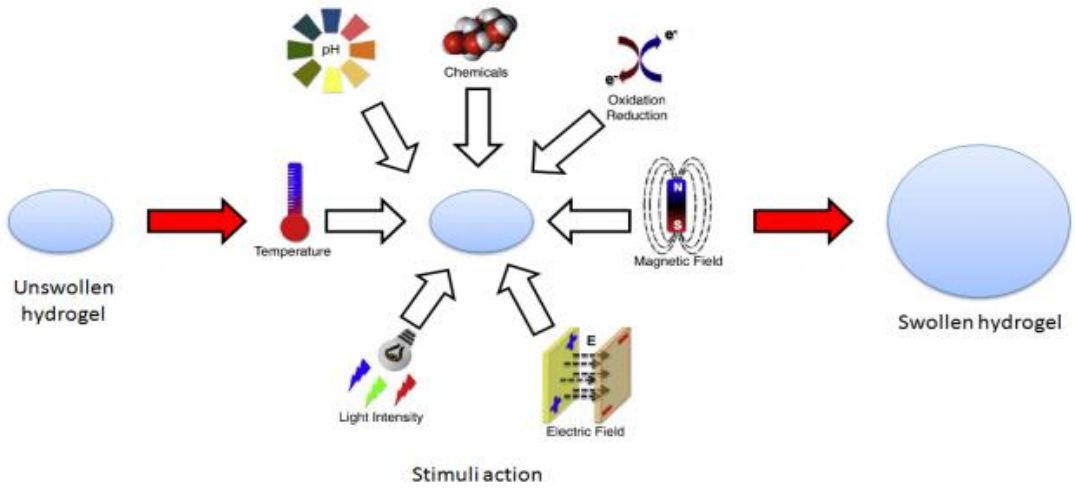

Figure 2.4: Stimuli responsive hydrogels (Tiwari et al, 2012)

2.2.2 pH Responsive Hydrogels

pH sensitive polymers are produced by adding acidic or basic functional groups to the polymer backbone. These functional groups either accept or release protons in response to appropriate pH and ionic strength changes in aqueous media (Langer and Peppas, 2003). The network porosity of hydrogels changes with electrostatic repulsion. As a result of changing the external pH, the ionic hydrogels that contain carboxylic or sulfonic acid groups gives either sudden or gradual changes in their equilibrium swelling behaviour. The number of acidic groups in the hydrogels contributes to the degree of ionization of these hydrogels, which results in increased electrostatic repulsion between negatively charged carboxyl groups on different chains. Thus increased in hydrophilicity of the network and greater swelling ratio at high pH. Conversely, hydrogels containing

basic groups, such as amines, ionize and show electrostatic repulsion at low pH (Zhang et al., 2005).

Acidic hydrogels, or ionic hydrogels, are unswollen at low pH as the acidic groups are protonated and unionised. Swelling is initiated when the environmental pH rises above the characteristic pKa of the acidic groups and the gel becomes ionised by deprotonation. Alternatively, basic hydrogels, or cationic hydrogels, exhibit swelling trend. Swelling occurs when the environmental pH falls below the pKa of the cationic groups and the gel is ionised by protonation. The network will stop swelling once the hydrogel has reached maximum ionisation. Any additional increase in pH will only increase the ionic strength, which will reduce osmotic pressure and result in deswelling or compression of the gel (Richter et al., 2008).

2.2.3 Temperature Responsive Hydrogels

Temperature responsive hydrogels are sensitive to the temperature and change their microstructural in response to change in temperature. These types of polymers are the most studied, most used and most safe polymers in drug administration systems and biomaterials. A very sensitive balance between the hydrophobic and the hydrophilic groups are present in thermos-responsive polymers in which small change in temperature can create new adjustment (Almeida et al., 2012).

Small temperature changes around a critical solution temperature (CST) make the chains collapse or extend, because of adjustments of the hydrophobic-hydrophilic interactions between the polymer chains and the aqueous medium as they present a fine hydrophobic-hydrophilic balance in their structure (Schmoljohann et al., 2003). A temperature at which the polymer solution undergoes separation from one phase to two phase also known as a critical solution temperature. Thus, these polymers undergo an

abrupt change in volume when the temperature of the medium is varied above or below the CST (Xu et al., 2006).

The polymers with lower critical solution temperature (LCST) are the most used on drug delivery systems as the therapeutics agents can be mixed with the polymer. When this is on its liquid state (temperature below the transition temperature) being able to be injected in the human body on the subcutaneous layer or in the damaged area. This will results to a gel deposit formed on the area where it was injected after increasing the temperature (Jeong and Gutowska, 2002).

2.3 Hydrogel Fabrication Technique

Hydrogels may be classified as homo-polymer, copolymer, semi-interpenetrating network (semi-IPN) and interpenetrating network (IPN) based on hydrogel fabrication technique Cross-linked networks of one type of hydrophilic monomer unit also known as homo-polymer hydrogel. Copolymer hydrogels are produced by cross-linking of two comonomer units, at least one of which must be hydrophilic to render them swellable. Whereas, interpenetrating polymeric hydrogels are produced by preparing first network and swollen in a monomer which the latter reacts to form a second intermeshing network structure.

2.3.1 Homo-polymeric Hydrogels

Polymer networks derived from single species of monomer also known as homopolymers. It is the basic structural unit and comprising of any polymer network (Iizawa et al., 2007). It may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique. Cross-linked homopolymers are widely used in drug delivery system and in contact lenses.

Poly(ethylene glycol) (PEG) based hydrogels are responsive towards external stimuli thus mostly used in drug delivery system. Chemically cross-linked PEG hydrogels are used as scaffolds for protein recombination and functional tissue production. It is proved to be a suitable biomaterial for the efficient and controlled release of drugs, proteins, biomolecules and growth factor (Lin and Anseth, 2009).

A new method of PEG hydrogel formation called 'Click' chemistry. This method based on a step-growth mechanism is distinguished by its rapid and specific reaction as well as versatility with respect to bio-conjugation. Macromers bearing azide and alkyne functional groups are 'clicked' together in the presence of catalyst. This lead to the formation of stable covalent linkages. The PEG hydrogels produced will have good mechanical properties and permits independent control of physical and chemical properties (Lin and Anseth, 2009).

Polyacrylic acid (PAA) is another homopolymeric hydrogel which contain 2.5% of PAA and 97.5% of water. It is stable and has optimal elasticity property. It was designed to be non-toxic, non-inflammatory and to imitate surrounding soft tissue when used as an endoprosthesis (Christensen et al., 2006).

2.3.2 Co-polymeric Hydrogels

Co-polymeric hydrogels are composed of two types of monomer in which at least one is hydrophilic in nature. PVP hydrogels can be obtained using different irradiation doses (5-15 KGy) and different additives: PEG with molecular weight of 600 and 6000, polyetheleneoxide (PEO) (400000) and glycerol. Glycerol and PEO used to reduce the cross-linking density of the PVP network. As for PEG, it will increase the elasticity of the gels as a result of the plasticizing effect. PVP/PEG hydrogels are sterile and non-cytotoxic, which make PEG an ideal addition to biomedical hydrogels designed as a dressing material (Das, 2013).

2.3.3 Semi-Interpenetrating Network (Semi-IPN)

Semi-interpenetrating network occur when one polymer is linear and penetrates another cross-linked network without any other chemical bonds between them (Zhang et al., 2009). Due to the absence of restricting interpenetrating elastic network, while providing the benefits like modified pore size and slow release of drug, semi IPNs can more effectively preserve rapid kinetic response rates to pH or temperature. To justify this, one example is the entrapment of linear cationic polyallylammonium chloride in acrylamide/acrylic acid copolymer hydrogel which imparted both higher mechanical strength and fully reversible pH switching of theophylline release. This pH sensitive semi-IPN was synthesized by N,N'-methylenebisacrylamide which acts as cross-linking agent (Zhang et al., 2005). The network contain both covalent and ionic bond. Three-dimensional structure of hydrogel is retained by the covalent bond. Whereas, the ionic bond give higher mechanical strength and pH responsive reversibility.

2.3.4 Interpenetrating Polymeric Network (IPN)

Two key features of IPN products are "interpenetrating" and "network", which lead to the characteristic of IPN chemical and mechanism properties. Schematic representations of IPN structure are shown in Figure 2.5. Different lines symbolize polymer chains that consist of different monomer units, whereas, dots are crosslinking or grafting sites between two polymers.

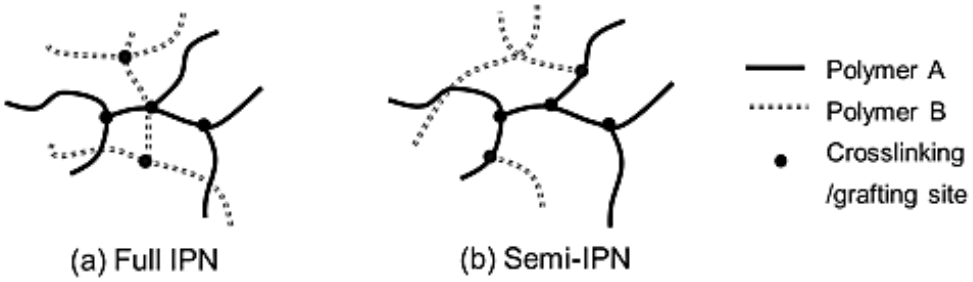

Figure 2.5: Schematic representations of IPN structure (Pacelli et al., 2014)

Figure 2.5 (a) illustrates the structure of the full IPN that has both polymers homo-crosslinked. The intimately combining crosslinked macromolecular network provide an advantages in controlling the phase separation. Even for polymers which are thermodynamically incompatible, permanent entanglements between the different crosslinked networks prevent complete phase separation in such system. Figure 2.5 (b) shows an example of semi-IPN (SIPN). This network only contains one polymer network. The other polymer presented in semi-IPN is linear or branched. There are semi-I and semi-II SIPN, which referring to the first or second polymers cross-linked, respectively. In fact, the formulation of the non-crosslinked polymer are important in SIPN phase behaviour. It is possible to separate the non-crosslinked polymer from the composites without permanent entanglements between the two polymers. Therefore, in order to reinforce the apparent compatibility, some degree of branched-structure is prefer in the system. The well-interpenetrated structure is thermodynamically more stable. Thus, the relationship between IPN crosslinking kinetics and IPN structure gives a great interests for product development.

Generally, to form an IPN, the reactants (monomers or polymers) are mixed together in solution and then the two networks can be formed either simultaneously or sequentially, according to the type of cross-linking reaction adopted for the two system. The IPN characteristics can be modified according to the concentration and type of

polymers used, as well as to the procedure followed during their preparation. For these reasons, they have drawn a lot of attention for the development of suitable materials for biomedical and pharmaceutical application (Pacelli et al., 2014).

IPNs usually show physical and mechanical properties intermediate of the constituent networks, thus the blending of a less-swell-able, stiffer hydrogel with more swell-able, softer hydrogel can be used to tune the IPN modulus and swell-ability. IPNs is the major improvement in toughness that often results. Enhances toughness is known to occur in IPNs known as “double network hydrogels” when the first network is more tightly crosslinked than the second network. Also, the molar ratio of the second network to the first network is greater than ~5 (Naficy et al., 2013).

Due to the permanent interlocking of network segments, IPN method can overcome thermodynamic incompatibility occurs and limited phase separation can be obtained. This network segments are believed to ensure stability of the bulk and surface morphology. Dense hydrogel matrices can be produced which feature stiffer and tougher mechanical properties, controllable physical properties and more efficient drug loading compared to any conventional hydrogels. Drug loading is often performed in conjugation with the polymerization of this phase. Other than that, IPN pore sizes and surface chemistries can be controlled to tune the drug release kinetics, interaction between the hydrogel and the surrounding tissues as well as its mechanical properties (Yin et al., 2007). Interpenetrating phases with varies degradation profiles and/or varies swelling responses o physiological conditions can be used to provide multiple controls over the swelling responses of hydrogels and thus the drug release kinetics (Li et al., 2007). Because of their ability to restrict the equilibrium swelling of either or both of the interpenetrating phases according to the elasticity, IPNs can moderate the effect of environmental changes on hydrogel responses and hence drugs burst release (Chivukula et al., 2006).

2.3.4.1. Double Network

A particular type of IPN is represented by the Double Network (DN) hydrogels, which differ from the conventional interpenetrating systems due to the existence in the same structure of two networks that are in sharp contrast in terms of rigidity, molecular weight and cross-linking density (Pacelli et al., 2014). This method is to obtain a very strong hydrogel by inducing a DN structure for various combinations of hydrophilic polymers. These DN hydrogels contain 60-90 % water and exhibit fracture strength as high as a few to several tens of mega Pascals. Besides show high wear resistance due to their extremely low coefficient of friction (Peppas et al., 2000).

The DN gels possess interpenetrating polymer network (IPN) structure where the properties of two networks existing in sharp contrast such as network density, rigidity, molecular weight, cross-linking density etc. DN gels is commonly obtained by following the two-step sequential free-radical polymerization process. The preparation of a stiff and brittle gel of polyelectrolyte is by immersed in an aqueous solution of the second monomer. The monomer will be cross-linked after the diffusion leasing to the formation of a second, soft and ductile network inside the gel. This approach will result to improved characteristic and mechanical properties due to a synergistic effect of binary asymmetric structure compare to the conventional IPN (Pacelli et al., 2014).

DN gels are an unique structural characteristics hydrogels as summarized by Gong's group: (1) the first network consists of rigid and brittle polymers (strong polyelectrolytes) and the second network consists of soft and ductile polymer; (2) the second network usually has 20-30 times higher of molar concentration compare to the first network; (3) the second network is loosely cross-linked; which require a very high molecular weight while the first network is often tightly cross-linked (Chen et al., 2015).

2.4 Hydrogel's Applications

Hydrogels represent an important class of biomaterials in biotechnology and medicine because of their excellent biocompatibility which give minimal inflammatory responses, thrombosis, and tissue damage (Graham, 1998). Hydrogels able to swell large amount of water without the dissolution of the polymer. This give hydrogel's physical characteristic that similar to soft tissues because of their hydrophilic and crosslinked structure. Other than that, they have high permeability for oxygen, nutrients, and other water-soluble metabolites. A number of hydrogels differing in structure, composition, and properties have been developed over the past three decades. This materials have been used extensively in medicine for applications such as contact lenses, biosensors, linings for artificial implants (Peppas et al., 2000).

2.4.1 Hydrogels for Drug Delivery

Treatment of diseases has always been a major issue for researchers as long as mankind has existed. Proteins, peptides, and other materials have been identified as "drugs" since technology has advanced which can be used to treat physiological life processes, pain and discomfort (Uchegbu et al., 2006). Drugs can vary in their characteristics to the extent that drugs used to treat the same symptoms might differ in characteristics such as hydrophilicity, chemical composition, size and effectiveness. As understanding of cellular biology at the molecular level increased and breakthroughs in proteomics have led to the concept of gene delivery (Langer et al., 2003). Drugs have to reach the site of action following administration (oral, intravenous, etc.) in a specific manner and in specific quantity which is the basis of drug delivery field. The delivery aims at delivering at right drug at the right place, at right concentration for the right period of time. Drug delivery can be difficult due to the treacherous route of delivery or discomfort caused to the patient (Uchegbu et al., 2006).

Oral administration has been considered to be most convenient routes of drug administration, and hence the majority of dosage forms are designed for oral delivery. Different types of hydrogels can be used for delivery of drugs to certain regions in the gastrointestinal tract ranging from the oral cavity to the colon, as shown in Figure 2.6.

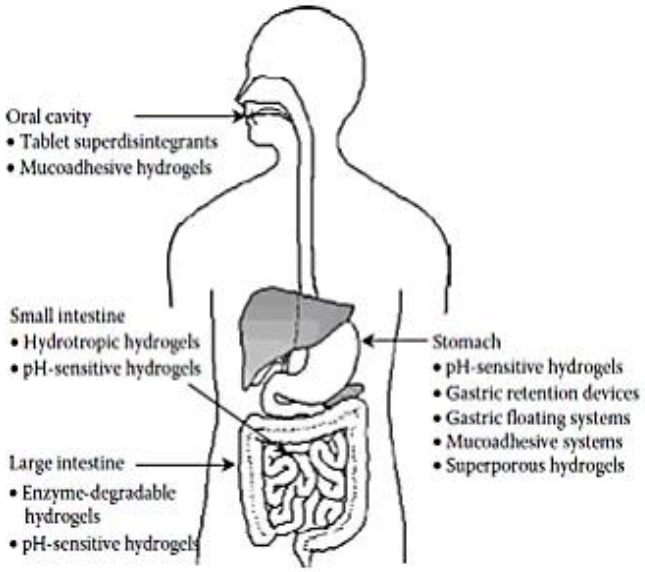

Figure 2.6: Various hydrogels and hydrogel formulations that can be used in different segments of the gastrointestinal tract for drug delivery (Uchegbu et al., 2006)

Hydrogels now play an important role in drug delivery. Drug release generally involves simultaneous absorption of water and desorption of drug via a swelling-controlled mechanism (Rao and Devi, 1988). The resistance of the polymer to an increase in volume and change in shape are the rate-controlling factor mediating drug delivery (Bouwstra and Junginger, 1993).

A glassy hydrogel which into contact with water or any other thermodynamically compatible medium will allows the solvent to penetrate into free spaces on the surface between the macromolecular chains. The glass transition temperature of the polymer drops to the experimental temperature as enough water has entered the matrix. The

presence of solvent in a glassy polymer causes the development of stresses that are accommodated by an increase in the radius of gyration and end-to-end distance of polymer molecules, which is seen macroscopically as swelling (Gupta et al., 2002).

Method of administering a pharmaceutical compound to achieve a therapeutic effect in or at a certain location in the human body also known as drug delivery (Nagai and Machida, 1993). Materials need to have controlled properties, such as absorption and release profile and no toxicity to be used as drug delivery systems (Banquy et al., 2009). PEG hydrogels can be used as biodegradable drug delivery systems, because of the biodegradable ester bond in the structure, the well-controlled structure and properties (Peppas et al., 1999). PEG is a FDA approved polymer for use inside the human body (Gong et al., 2009). PEG can be used to form a hydrogel in situ via TEC because of the low toxicity of its precursors and crosslinkers. The seqIPN PEG hydrogels help to enhance the mechanical properties to suit the application. Figure 2.7 pictures a diagram of degradable PEG hydrogel as a drug-delivery system.

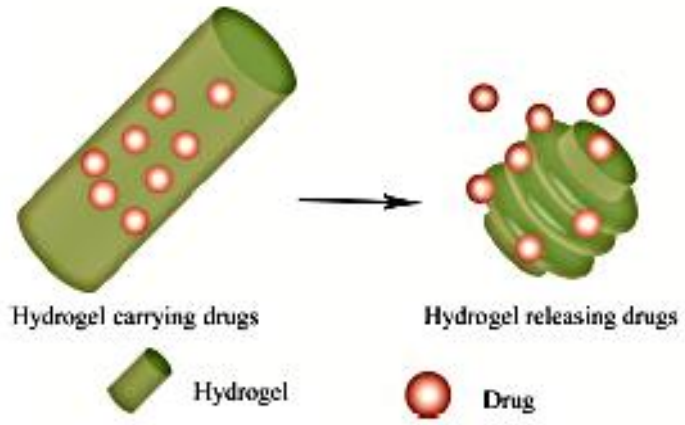

Figure 2.7: Diagram of a drug-delivery system uses a biodegradable PEG hydrogel carrying drugs and releasing at certain location (Thakur et al., 2017)

The high porosity of hydrogels can easily be adjusted by controlling the density of cross-links in their matrix and the affinity to water. Drugs can be loaded and then released due to their porous structure. The advantages offered by hydrogels include the possibility for sustained release, which results in maintaining a high local concentration of an active pharmaceutical ingredient over a long period (Thakur et al., 2017). The drug can be loaded into a hydrogel and then its release may proceed through several mechanisms: diffusion controlled, swelling controlled, chemically controlled and environmentally controlled-responsive release.

Hydrogels as cell adhesion resistant surface have been used to prevent thrombosis after surgery. It have compatibility with blood and other body fluids. Thus, their application can be extended for forming contact lenses, wound dressings, membranes, and as coating applied to living tissue surface. Hydrogel can encapsulate cells. This will allow them to proliferate, differentiate, and organize, indicating their potential in tissue engineering scaffolding. If hydrogels of various functionalities can be developed, different biomedical requirements can be meet. Stimuli-sensitive hydrogels can respond to changes in various parameters such as pH and temperature to achieve controlled drug release. For example, the digestive tract has a pH range from 4-8 which a pH sensitive hydrogel can be design to controlled drug release. Hydrogel based delivery can be used for epidermal and subcutaneous application. Hydrogels exhibit tissue adhesiveness are important in application such as closure wound healing for various tissues or organs. This properties can be used for drug delivery through mucus membranes to achieve non-invasive drug administration (Veronese et al., 1999).