# CHAPTER II
# LITERATURE REVIEW

## 2.1 Conductive polymer (CP)

A conductive polymer is one type of polymers that is capable of conducting electricity. Most polymers are insulators, meaning they do not conduct electricity well. Thus, the electrical conductivity of polymer is enhanced by a process called doping, in which other elements (dopant) are added to the host polymer matrix. There are two types of dopant, n-type (electron donating) and p-type (electron acceptor). The n-type doping, using reducing agent for adding electrons to the conductive band can generate negative charges which can be delocalized as a charge carrier. The p-type doping, using oxidizing agent for removing electrons from the conductive band can generate positive charges which can be delocalized as a charge carrier. The resultant conductive polymer, after the process of doping, will have a high electrical conductivity because the pristine polymer is transformed from insulating to metallic (Chansai *et al.*, 2009).

The electrically conductive polymer is composed of conjugated polymer chain with π-electrons delocalized along the backbone. There are several families of conductive polymer such as polyacetylene, polythiophene, polypyrrole, poly(p-phenylene), polyaniline, polyfluorene, poly(3,4-ethylenedioxythiophene), poly (phenylene vinylene), and poly(thiophene vinylene) as shown the repeating units in figure 2.1.

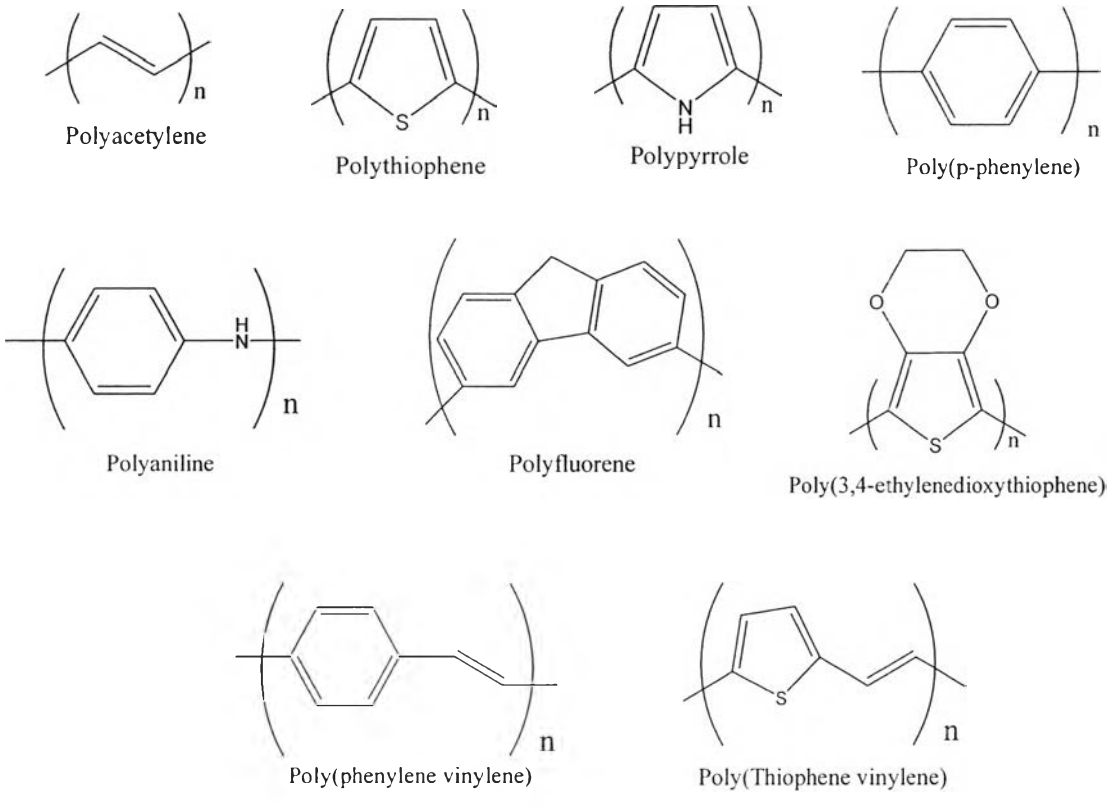


**Figure 2.1** The repeating units of some conductive polymers.

There are many applications of conductive polymer including batteries, silicon replacement, light-emitting diodes, microtools, capacitors, smart windows, light emitting diodes, transistors, photovoltaics, microlithography, corrosion control, conductive adhesives and inks, static dissipation, EMI shielding, radar/microwave absorption, direct plating, electro-static powder coating, clean room applications, sensors, medical electrodes, and controlled release systems (Kuhn *et al.* 1995).

Stassen *et al.* (1995) investigated the poly(3-hexylthiophen) as a composite membrane comprising a conductive polymer as an active separation layer for potential using in drug delivery system. Dopamine, a neurotransmitter, was chosen for testing this new composite membrane and the transport of dopamine was more permeable in the reduced state, whereas in the oxidized form permeability decreased by 40%. The ion signal of dopamine was highest in a film thickness of 3 μm.

Kontturi *et al.* (1998) studied the controlled release of anionic drug, salicylate, naproxen and nicoside, using the conductive polymer, polypyrrole (PPy), as an ion gate membrane. The electrochemical quartz crystal microbalance (EQCM) was used to measure the mass changes and HPLC to determine the release of drugs from the membranes. The amount of drug stored inside the membrane and the amount which can be released were dependent on the molecular size and structure of the drug, and the procedure of the polymerization of the membrane. More anions were released when the negative going pulse was higher or the time of reduction was longer.

Kontturi *et al.* (1998) investigated the optimum conditions of polypyrrole membrane for the release of anionic drugs, sodium *p*-toluene sulfonate (NaTOS), by using EQCM and prepared PPy ion-gate membranes by the electrochemical polymerization. When potential was below about 800 mV, the polymerization occurred slowly and the structure of membrane was so tight; bigger anion, $TOS^-$, was difficult to diffuse. At a potential above 900 mV, the membrane had more open structures, the $TOS^-$ ion moved easily. Release of anion during the reduction of the PPy should yield a pH value below about 7. There were no significant effects of temperature and permittivity of the solution on ion exchange property of polypyrrole membrane. The impendent measurements confirmed that ion transport when the membrane was in the charged state and in the reduced state the membrane was an insulator and almost no ion transport occurred.

Moretto *et al.* (2004) studied the slower release of two antibiotics, tylosin tartrate and oxytetracycline hydrochloride in poly(vinyl alcohol) (PVA) hydrogels ($M_W$ = 31,000-50,000). It was found that at a lower drug matrix loading (10 mg/ml), the invitro release rate of both antibiotics could be reduced by a previous freeze drying of the gel, while no reduction in drug rate took place in heavily loaded matrices (300 mg/ml). When PVA hydrogels containing tylosin were administered to rats, the drug could not be detected in the blood, but it was found in organs: liver, kidneys, and muscles, for up to 120 h. On the other hand, when the same amount of drug was administered orally as powder, no appreciable organ accumulation was detected, while the drug was found in feces and urine. These data show that PVA hydrogels could be a suitable slower release system for tylosin administration.

Oxytetracycline could also be quantitatively entrapped and released from PVA hydrogels, but once administered through mouth to rats, it was not detected in blood or organs.

Wadhwa *et al.* (2006) investigated electrically controlled release of an anti-inflammatory drug, dexamethasone (Dex), from PPy coating on the electrode sites. The drug was incorporated in PPy via the electropolymerization of pyrrole and the release in phosphate buffer saline using cyclic voltammetry (CV). FTIR analysis of the surface showed the presence of Dex and PPy on the coated electrode. The thickness of the coated film was estimated to be ~50 nm by ellipsometry. They were able to release 0.5 $\mu g/cm^2$ Dex in 1 CV cycle and a total of almost 16 $\mu g/cm^2$ Dex after 30 CV cycles from a 50 nm thick PPy/Dex film.

Gade *et al.* (2007) synthesized PPy by the electrochemical polymerization with different electrolytes such as potassium nitrate, sodium nitrate, sulphuric acid, hydrochloric acid, potassium chloride, sodium chloride, oxalic acid, and sodium salicylate. They used the galvanostatic method over wide ranges of pH of the reaction medium and applied current density. They investigated the influence of electrochemical process parameters such as monomer and electrolyte concentrations, current density, pH of the electrolyte, and type of electrolyte on the polymerization of PPy. They indicated that the conductivity depended on the anion present in the electrolytes which followed the order $NO_3^- > Cl^- > COO^-$, and as the plateau potential increased there was a decreasing in the conductivity. The PPy film synthesized at pH 3.0 with applied current density of 1 $mA/cm^2$ resulted in a uniform, porous, and microglobular surface morphology with enhanced electrical conductivity. The polymerization potential increased with the pH and applied current density.

Barthus *et al.* (2008) blended the electrochemical polymerization of PPy into polyacrylamide (PAAM) hydrogel for controlled release. The influences of several parameters in the synthesis, such as type of hydrogel matrix and polymerization conditions were studied using a fractional factorial design. For controlled release tests, safranin was used as model drug and release curves (amount of drug versus. time) indicated that these blends were promising materials for using in controlled release.

Luo *et al.* (2009) developed nanoporous PPy for an electrochemically controlled drug release system. PPy and a model drug, fluorescein, were electrochemically copolymerized on glassy carbon (GC) electrodes modified with self-assembled multilayer polystyrene (PS) nanobeads, and PPy films incorporated with fluorescein as dopants were formed among the interstitial spaces of the tightly packed PS nanobead template. After the removal of the PS hard template, nanoporous PPy films incorporated with the drug fluorescein were obtained. Due to the porous morphology and huge surface area, the efficiency of the prepared PPy films in electrochemically releasing incorporated fluorescein was about nine times higher than that of conventional PPy films.

Nart *et al.* (2011) synthesized poly(acrylic acid-co-2-hydroxyethyl methacrylate-co-2-acrylamido-2–methyl-1–propanesulfonic acid (AAc-HEMA-AM PS) microgels using an inverse suspension polymerization technique. Lidocaine (LD) and methylene blue (MB) were used as model drugs. The increase in the AMPS content of the microgels composition caused a larger increasing in water uptake. The AMPS containing microgels had a mean particle diameter of 10 μm. Results of this work allowed a conclusion that the lower molecular weight character of LD increased the drug loading as compared to MB. The amount of initial burst values decreased as the AMPS content of the microgel increased and the slower drug release pattern was attained. However, the specific interactions between MB and the microgel matrix led to pH dependent release model.

Tsai *et al.* (2011) prepared electro-conductive hydrogels based on poly(vinyl alcohol), crosslinked with diethyl acetamidomalonate as the hydrogel component using polyaniline as the conductive component for drug delivery, indomethacin as the model drug. The hydrogels were characterized for their physicochemical and physicomechanical properties. Drug entrapment efficiency ranged from 65-70%. "ON-OFF" switchable drug release was obtained by periodically applying-removing-reapplying an electric potential ranging from 0.3-5.0 V for 60 seconds at hourly intervals and the cumulative drug release obtained ranged from 4.7-25.2% after four release cycles, respectively. The electro-stimulated release of indomethacin was associated with the degree of crosslinking, polymeric ratio, and drug content.

Esrafilzadeh *et al.* (2013) synthesized poly(3,4-ethylenedioxythiophene) and poly(styrenesulfonate) (PEDOT:PSS) fiber, which served as the inner core to the electropolymerized outer shell layer of PPy. Ciprofloxacin hydrochloride (Cipro) was selected as the model drug and as the dopant in the PPy synthesis. The release of Cipro in phosphate buffered saline (PBS) from the fibers was controlled by switching the redox state of PPy Cipro layer. Release of Cipro under passive and stimulated conditions were tested against Gram positive (Streptococcus pyogenes) and Gram negative (Escherichia coli) bacteria. Significant inhibition of bacterial growth was observed against both strains tested. These results confirm that Cipro retained antibacterial properties during fiber fabrication and electrochemically controlled release. In vitro cytotoxicity testing utilizing the neural B35 cell line confirmed the cytocompatibility of the drug loaded conducting fibers.

## 2.2 Polythiophene

Polythiophene (PTh) is one the most important classes of conjugated polymers which results from the polymerization of thiophenes, a sulfur heterocycle. PTh has been widely used as environmentally and thermally stable conjugated polymer materials, such as chemical and optical sensors, light-emitting diodes and displays, photovoltaic devices, molecular devices, DNA detection, polymer electronic interconnects, solar cells, and transistors (Lin *et al.*, 2009). Due to the electron-rich character of the thiophene ring, PTh can be easily and reversibly oxidized by a chemical or electrochemical polymerization that leads to the p-doped type, usually a highly conducting material.

There are several routes for the synthesis of polythiophene: (1) electropolymerization, (2) metal-catalyzed coupling reactions, and (3) chemical oxidative polymerization. The chemical oxidative polymerization is a better route for the polymerization of PTh because it gives A higher yield (Kamat *et al.*, 2012). The thiophene and PTh structures are shown in figure 2.2.


Thiophene Polythiophene

**Figure 2.2** The structure of thiophene monomer and polythiophene.

Sari *et al.* (2002) synthesized polythiophene by electrochemical method using three different supporting electrolytes ($LiClO_4$, $Et_4NBF_4$, $Bt_4NPF_6$) and two different solvents (acetonitrile and benzonitrile) in AN anhydrous medium. PTh ($LiClO_4$) showed the highest conductivity AT 0.35 S $cm^{-1}$ with the acetonitrile solvent medium. PTh ($Et_4NBF_4$) showed the highest conductivity at 0.54 S $cm^{-1}$ with the benzonitrile solvent medium. Then, polyurethane/polythiophene (PU/PTh) conducting copolymers were prepared using PU as an insulating matrix, their structures and properties were analyzed. The electrochemical properties of polymers were investigated by cyclic voltammetry (CV). The conductivities of polymers were measured by four probe technique. It was found that all homopolymers and bipolymers were of conducting mechanism from the Gouy balance magnetic measurements. Thermal analyzes of the polymer films was done by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). From thermal analyses, it was found that among the PThs, PTh ($Et_4NBF_4$), and among the copolymers PU/PTh ($Et_4NBF_4$) showed the highest thermal stability as 191 °C and 210 °C, respectively.

Abou-Elenien *et al.* (2004) studied stability and electrical conductivity of PTh films by using several electrochemical techniques and different solvents. The most stable polythiophene film showed the lowest relaxation time when using galvanostatic technique in acetonitrile solvent with $TBAPF_6$ as the supporting electrolyte at 5 °C. As the donor number of the solvent increased, the relaxation time decreased. Temperature was also shown to affect the relaxation time.

Tuken *et al.* (2005) showed that the electrochemical synthesis of homogeneous and stable PTh film could not be achieved on copper electrode, by

direct electro-oxidation of thiophene in ACN-$LiClO_4$. This prevented the deposition of a homogeneous polymer film on the surface. The copper sample was coated with thin PPy film in an aqueous oxalic acid solution. Then, the synthesis of PTh top coating was achieved. The obtained PPy/PTh coating was found to have very low permeability against the attack of corrosive environment and exhibited more effective barrier property for considerable immersion period in 3.5% NaCl solution. It could also provide some anodic protection, by modifying the copper corrosion products.

Lee *et al.* (2008) fabricated unsubstituted PTh via the $Fe^{3+}$-catalyzed oxidative polymerization in aqueous dispersion. The dispersion state showed that the PTh nanoparticles were well dispersed in many polar solvents, compared to non-polar solvents. The photoluminescence intensity of PTh nanoparticle dispersion prepared by the $Fe^{3+}$-catalyzed oxidative polymerization was much higher than bulk PTh. Photoluminescence intensity of the core-shell poly(styrene/thiophene) nanoparticle dispersion was much higher than that of the PTh nanoparticle dispersion, due to its thin shell layer morphology, which was explained by the self-absorption effect.

Lee *et al.* (2008) demonstrated that the unsubstituted thiophene can be polymerized by the $Fe^{3+}$-catalyzed oxidative polymerization inside nanosized thiophene monomer droplets, dispersed in aqueous medium under acidic solution conditions with anionic surfactant. This facile method included a $FeCl_3/H_2O_2$ (catalyst/oxidant) combination system, which guaranteed a high conversion (ca. 99%) of thiophene monomers with only a trace of $FeCl_3$. The average particle size was about 30 nm, within a narrow particle-size distribution (PDI = 1.15), which resulted in a good dispersion state of the unsubstituted polythiophene nanoparticles. Hansen solubility parameters were introduced to interpret the dispersion state of the polythiophene nanoparticles with various organic solvents. The UV–Visible absorption and photoluminescence (PL) spectrum were measured to investigate the light emitting properties of the prepared unsubstituted polythiophene nanoparticle emulsions. According to non-normalized PL analysis, the reduced total PL intensity of the polythiophene nanoparticle emulsions can be rationalized by the self-absorption in a wavelength range less than 500 nm.

Gnanakan *et al.* (2009) synthesized PTh nanoparticles by a cationic surfactant assisted dilute polymerization method. The polymer nanoparticles was used as electrode materials for symmetric type high performance redox super capacitor studies with PVdF-co-HFP based microporous polymer electrolyte containing 1 M $LiPF_6$ in 1:1 EC/PC electrolyte. Its specific capacitance was found to be 134 F/g. This capacitance slowly decreased on continuous cycling, due to both the polymer degradation and mechanical stress on the PTh. The PTh obtained by the cationic surfactant assisted dilute polymerization method had better capacitor performances than the same obtained by the conventional chemical and electrochemical polymerization methods.

Kelkar *et al.* (2011) fabricated PTh by using catalytic coupling of the Grignard reagent of 2,5-dibromothiophene and nickel salt. In addition, PTh was doped with $FeCl_3$ for 2.5, 5, and 10 h. For structural investigation, all samples were characterized using different techniques. The results of elemental analysis showed that with the increase of doping duration the iron content increased while the sulphur content decreased. Glass transition temperature ($T_g$) decreased after doping, indicating that dopant acts as a plasticizer. Thermal stability, in general, increased due to doping.

Senthilkumar *et al.* (2011) prepared PTh by the chemical oxidative polymerization method in presence and absence of three different (cationic - CTAB, anionic - SDS, and non-ionic - Triton X-100) surfactants using $FeCl_3$ as oxidant. The functional groups, n-$\pi^*$ electronic transition of the conjugated molecules and $\pi$-$\pi$ stacking structure of PTh were identified by FT-IR, UV–Vis, and XRD, respectively. The SEM image elucidated the morphological features of PTh. Spherical like morphology was observed for PTh prepared using the anionic surfactant. The specific capacitances (SC) were calculated and the PTh prepared with Triton X-100 provided higher SC of 117 F/g which was higher (up to 33%) compared to SC of surfactant free PT (78 F/g). Thus, the PTh prepared in presence of Triton X-100 was found to be the suitable electrode materials for redox super capacitors.

Kamat *et al.* (2012) studied deposition PTh thin films on glass substrate by the chemical bath deposition method using $FeCl_3$ as an oxidant and chloroform as a solvent. The variation of oxidant concentration strongly affected the properties of

these films. The thickness, absorbance, band gap, and refractive index of the films increased whereas the transmittance decreased due to increase in oxidant concentration.

## 2.3 Hydrogel

Hydrogels are polymeric networks that can be absorb larger quantities of water while remaining insoluble in aqueous solutions due to chemical or physical crosslinking of individual polymer chains. Hydrogels can be classified as neutral or ionic, based on the nature of the side groups (neutral or ionic), the method of preparation (homo- or co-polymer), the physical structure (amorphous, semicrystalline, hydrogen bonded, supermolecular, and hydrocollodial), and the responsiveness to physiologic environment stimuli (pH, ionic strength, temperature, electromagnetic radiation, etc.) (Peppas *et al.*, 2004).

Hydrogels can be prepared form natural or synthetic polymers. Although hydrogels made from natural origins, they may not show good mechanical properties and may exert immunogenicity or evoke inflammatory responses due to the presence of immunogen/pathogen moieties. However, they offer various advantageous properties such as being usually non-toxicity, biocompatibility, and showing a number of remarkable physicochemical properties that make them suitable for different applications in drug delivery systems. In comparison, the well-defined structure of synthetic polymers may lead to hydrogels with well-defined and fine-tunnable degradation kinetics as well as mechanical properties (Hamidi *et al.*, 2008).

Generally, three parameters are critical in describing the structure of crosslinked hydrogel network: 1) the polymer volume fraction in the swollen state, $\upsilon_{2,s}$ ; 2) number average molecular weight between crosslinks, $\overline{M}_c$ ; and 3) the mesh size, $\xi$. The mobility of encapsulated molecule and their rates of diffusion within a swollen hydrogel matrix are determined by the distance between polymer chain and the flexibility of those chain together (Lin *et al.*, 2006).

The membranes were prepared and their polymer volume fraction in the relaxed is calculated using Eq. (2.3). After each membrane swollen to equilibrium at

37 °C, the polymer volume fraction of the swollen polymer was calculated using Eq. (2.4):

$$\upsilon_{2,r} = \frac{V_d}{V_r} \tag{2.3}$$

$$\upsilon_{2,s} = \frac{V_d}{V_s} \tag{2.4}$$

where $V_d$ = the volumes of the polymer sample in the dry states

$V_r$ = the volumes of the polymer sample in the relaxed states

$V_s$ = the volumes of the polymer sample in the swollen states

$\upsilon_{2,r}$ = the polymer volume fractions of the relaxed polymer gel

$\upsilon_{2,s}$ = the polymer volume fractions of the swollen polymer gel

The volumes of the polymer sample in the dry, relaxed, and swollen states are calculated using Eqs. (2.5) - (2.7), respectively:

$$V_d = \frac{W_{a,d} - W_{h,d}}{\rho_h} \tag{2.5}$$

$$V_r = \frac{W_{a,r} - W_{h,r}}{\rho_h} \tag{2.6}$$

$$V_s = \frac{W_{a,s} - W_{h,s}}{\rho_h} \tag{2.7}$$

where $W_d$ = the weights of the dry polymer in air and heptane

$W_r$ = the weights of the relaxed polymer in air and heptane

$W_s$ = the weights of the swollen polymer in air and heptane

$\rho_h$ = the density of heptane

The swelling ratio ($Q$) was determined from the weight measurement using Eq. (2.8):

$$Q = \frac{1}{\upsilon_{2,s}} \tag{2.8}$$

The molecular weight between crosslinks, $\overline{M}_c$, was calculated from the swelling data using Eq. (2.9):

$$\frac{1}{\overline{M}_c} = \frac{1}{\overline{M}_n} - \frac{\frac{\bar{v}}{V_1}\left[\ln(1-v_{2,s}) + v_{2,s} + \chi v_{2,s}^2\right]}{v_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{v_{2,s}}{v_{2,r}}\right)\right]} \tag{2.9}$$

where $\overline{M}_n$ = the number-average molecular weight of the polymer before crosslinking

$\bar{v}$ = the specific volume of carrageenan

$V_1$ = the molar volume of water (18.1 $cm^3$/mol)

$x$ = the Flory interaction parameter of carrageenan and the dissociation constant is pKa = 4.7.

In general, the presence of carrageenan leads to a more open network structure and results in a higher $\overline{M}_c$ value. The hydrogel mesh size, ξ, was calculated using Eq. (2.10) (Peppas and Wright, 1996):

$$\xi = \upsilon_{2,s}^{-1/3}\left[C_n\left(\frac{2\bar{M}_c}{\bar{M}_r}\right)\right]^{1/2} \cdot l \tag{2.10}$$

where $C_n$ = the Flory characteristic ratio for carrageenan

$l$ = the carbon-carbon bond length of the monomer unit

The crosslinking density of the hydrogel, $\rho_x$, was calculated by using Eq. (2.11) (Peppas *et al.*, 1996).

$$\rho_x = \frac{1}{\bar{v}\bar{M}_c} \tag{2.11}$$

The degree of swelling and the weight loss of hydrogel were measured in a MES buffer solution at 37 °C for 2 days, using the following Eqs. (2.12) and (2.13):

$$\text{Degree of swelling (\%)} = \frac{M - M_d}{M_d} \times 100 \tag{2.12}$$

and

$$\text{Weight loss (\%)} = \frac{M_i - M_d}{M_i} \times 100 \tag{2.13}$$

where M = the weight of the sample after immersing in the buffer solution

$M_d$ = the weight of the sample after immersing in the buffer solution in its dry state

$M_i$ = the initial weight of the sample in its dry state

## 2.4 Carrageenan

Carrageenans are linear, anionic, partially sulfated galactans extracted from many species of red algae, seaweed found throughout the coasts of North America and Europe. They are composed of d-galactose residues linked alternately with α-(l→3) and β-(l→4) linkages. These sulfated galactans are classified according to the presence of 3,6-anhydrogalactose on the 4-linked residue and the position and number of sulfate groups (Pavli *et al.*, 2010). The most important types of carrageenans are κ-, i- and λ-carrageenan (Figure 2.3).

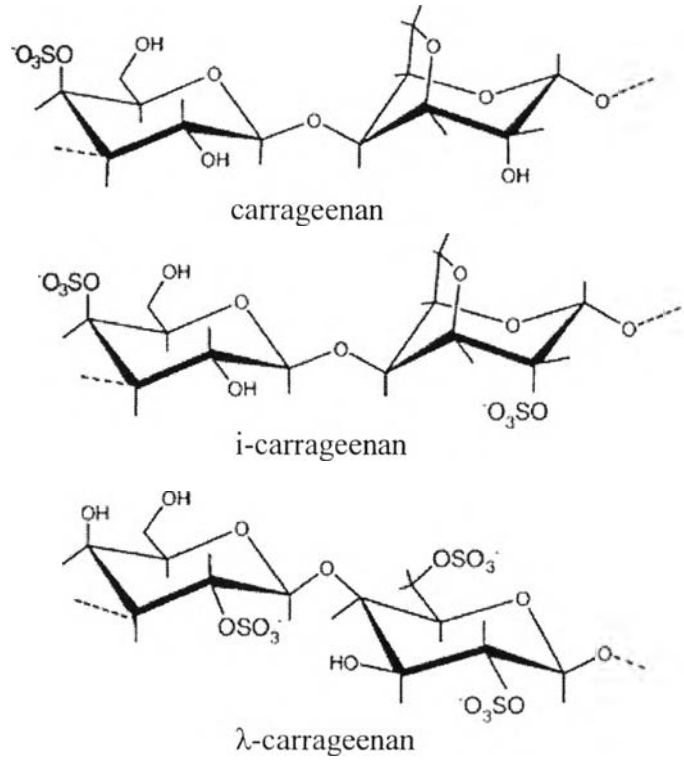


**Figure 2.3** The repeating unit structure of the carrageenan family.

Carrageenan is gelled by salts such as KCl, but it can form a gel under salt-free conditions also. κ-carrageenan only shows gel-forming characteristics in water. Potassium and calcium ions induce the gelation, while sodium does not. In the i-carrageenan, the gelation occurs in the presence of calcium ions. At low temperature and higher salt concentration, a double helical arrangement of the parallel polysaccharide chains can be formed. The temperature for gelation is about 25 °C, and remelting occurs at 35 °C.

Carrageenans are very often used in food products as thickeners and stabilizers. Using in salad dressings, prepared meat and fish, flavored milk, processed cheese, ice cream, evaporated milk, cream, cottage cheese, sour cream, infant formula, alcoholic beverages, sauces, and dressings. However, their usage is also increasing in pharmaceutical formulations. The polyanionic nature of carragenans was shown to have a possible crucial influence on drug release behavior as well (Singh *et al.*, 1998).

Moreover, κ-carrageenan has been used to prepare one component of the blend of two different natural polymers, agar and gelatine, and tested for the release

of theophylline (TPH) as a model drug. The releases of TPH from hydrogels are dependent upon the composition of the hydrogel, the type of component, and the possible interactions between two component polymers, as well as external temperature. The most relevant effect was found in the gelatin-κ-carrageenan blend in the 1:1 ratio (Liu *et al.*, 2005).

Sipahigil *et al.* (2001) prepared and assessed carrageenan beads as a controlled release system for verapamil hydrochloride and ibuprofen. Beads were prepared by an ionotropic gelation method. The encapsulation efficiency of veraparnil HCl in the beads (34.8–71.1%) was higher than that of ibuprofen (23.6–58%). While about 30% of ibuprofen was released at 6 h, about 70% of verapamil HCl was released in 5 h from the carrageenan beads prepared.

Naim *et al.* (2004) studied the effect of potassium chloride (KCl) and a cationic drug, metformin HCl, on swelling, erosion and release from κ-carrageenan matrices. Water uptake by the matrix up to 2 h was found to increase with KCl concentration from the plain matrix. Erosion was not affected by concentration of KCl. Incorporation of drug favored water uptake, but in presence of KCl it was reduced. Drug-containing matrices had shown higher release with KCl added as compared to plain batches. In the presence of metformin HCl, the cohesivity of matrices was reduced above 5% wt/wt KCl content causing an increase in drug release.

Mohamadnia *et al.* (2007) designed of pH-sensitive IPN hydrogel beads of carrageenan-sodium alginate (Caralgi) for controlled drug delivery and used betamethasone acetate as a model drug. Maximum loading efficiency (71%) was achieved at pH 4.8 and 55 °C. The chemical structure and morphology of the hydrogels with and without drug were studied using FTIR and SEM analyses. Loading efficiency depended on the pH and temperature. The in vitro release behavior by Caralgi IPN samples, prepared under various conditions, was evaluated and compared with that of the non-IPN alginate-$Ca^{2+}$ and carrageenan-$K^{+}$ hydrogels at pH 1.2 and 7.4.

Piyakulawat *et al.* (2007) prepared polyelectrolyte beads from chitosan (CS) and carrageenan (CR) for controlled release by using sodium diclofenac (DFNa) as a drug. CS/CR proportion, DFNa content, types and amount of crosslinking agents

affected the drug release. The optimal formulation was obtained with CS/CR proportion of 2/1 and 5% (wt/v) DFNa. The beads crosslinked with glutaric acid showed better results than the non-crosslinked beads, and the beads crosslinked with glutaraldehyde were the best with regards to the effectiveness for prolonged release of the drug over 24 h It was also observed that the release of diclofenac was higher at pH = 7.4 than pH = 6.8 and 1.2.

Prado *et al.* (2008) developed κ-carrageenan interpolyelectrolyte complex (IPEC) by using basic butylated methacrylate copolymer. Turbidity measurements and an elemental analyzes pointed to a 1:1 interaction of the repeating units. The formation of IPEC was confirmed by FTIR. Electronic microscopy images, particle size determination by image analysis and $N_2$ (77 K) adsorption measurements were consistent with a porous material. This IPEC formed presented very good flow ability and compactibility. Two maxima were observed in the swelling behavior as a function of pH. Release profiles were properly represented by a mathematical model, which indicated that the system releases ibuprofen in a zero-order manner. These profiles could be controlled by conveniently modifying the proportion of the IPEC in the tablets.

Keppeler *et al.* (2009) prepared crosslinked carrageenan beads for controlled release delivery system. Both bulk polymer concentration and crosslinker concentration influenced the bead size. The mechanism of crosslinking between epichlorohydrin and the polysaccharide was evaluated. The conditions were optimised on macroparticles (3.1 mm in diameter) for suitable crosslink density and its effect on the morphology and surface topography of the bead. It was shown that lower epichlorohydrin concentrations led to unstable and weak beads with rough and cracked surfaces. The optimum crosslinker concentration, which resulted in smooth and stable gel beads, was applied to microparticles (76 μm in diameter). The swelling/shrinking behavior of these crosslinked microgels in saline solutions showed great potential for the application of these micro-sponges as delivery systems in food or pharmaceutical products.

Rasool *et al.* (2010) prepared a silane crosslinked hydrogel between κ-carrageenan (KC) and acrylic acid (AA) application for insulin delivery using vinyltriethoxysilane (VTESi) as a crosslinker. The structural analysis of the hydrogel

confirmed the presence of the feed components in the hydrogel. Thermal stability of the hydrogel was increased by increasing the amount of AA or crosslinker content in KC/AA hydrogel. The decrease in swelling ratio was suggested to be due to the increase in AA content and crosslinker. Most promising results with high swelling ratio were observed in hydrogel having a lower monomeric ratio (KC:AA = 1:7). pH response of this hydrogel in acidic and neutral pH made its suitable for drug delivery application. A sustained release of insulin was observed in a simulated intestinal fluid (SIF) with negligible release of insulin in simulated gastric fluid (SGF).

Leong *et al.* (2011) prepared insulin entrapped in lectin-functionalized carboxymethylated κ-carrageenan microparticles. The encapsulation of insulin was performed using an ionic gelation technique and optimized to give an encapsulation efficiency of 94.2 ± 2.6% and a drug-loading capacity of 13.5 ± 0.4%. The microparticles were further surface-lectin-functionalized for improved intestinal mucoadhesiveness. The oral administration of insulin entrapped in the microparticles led to a prolonged duration of the hypoglycemic effect, up to 12–24 h in diabetic rats.

Muhamad *et al.* (2011) prepared κ-carrageenan/sodium carboxymethyl-cellulose beads based on different blend formulations using genipin, a crosslinking reagent. Different genipin concentrations (0.5, 1.0, 1.5 mM) were used to study the effects on swelling ratio of the beads in different pH values under simulated gastrointestinal tract condition (pH 1.2 and 7.4). The results showed that the cross-linked beads possessed lower swelling ability in all pH conditions and swelling ratio decreased with increasing genipin concentration. Moreover, the release of beta-carotene was slower and lesser after being crosslinked. A microstructure study showed that crosslinked beads exhibited a smoother surface and a more spherical shape compared to the native beads. This indicated that crosslinking of genipin had enhanced the beads network stability and their structure to be applied as suitable hydrogel.

Pavli *et al.* (2011) investigated interactions between doxazosin mesylate (DM) as the cation drug and carrageenans by using a DM ion-selective membrane electrode. The interaction between doxazosin cations, $DH^+$, and carrageenans was cooperative. At lower drug concentrations, an aggregation of $DH^+$ depended on initial strong electrostatic interactions. The strength of interactions increased with

increasing negatively charge of carrageenans. At saturation, the number of DM molecules bound per repeat unit depended on the charge and steric distribution of binding sites on carrageenans. Drug release rates of DM from carrageenan matrices were in accordance with the cooperativity binding constants.

Kulkarni *et al.* (2012) synthesized pH-responsive interpenetrating network (IPN) hydrogel beads of polyacrylamide grafted j-carrageenan (PAAm-g-CG) and sodium alginate (SA) by simple ionotropic gelation/covalent crosslinking technique for the intestinal delivery of ketoprofen. The PAAm-g-CG was synthesized by a free radical polymerization followed by an alkaline hydrolysis under nitrogen gas. The PAAm-g-CG was characterized by the elemental analysis, the FTIR spectroscopy, and the thermogravimetric analysis (TGA). The amorphous nature of drug in the beads was confirmed by the differential scanning calorimetry and the X-ray diffraction studies. The spherical shape of the beads was confirmed by scanning an electron microscopic analysis. The beads exhibited anample pH-responsive behavior in the pulsatile swelling study. The ketoprofen release was significantly increased when pH of the medium increased. The drug release depended on the extent of crosslinking in the IPN matrix. Stomach histopathology of albino rats indicated that the prepared beads were able to retard the drug release in stomach leading to the reduced ulceration, hemorrhage, and erosion of gastric mucosa.

## 2.5 Drug Delivery System (DDS)

Drug delivery is the method of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals during a desired period and at a specific rate. It is imperative that the drug concentration in the blood be maintained at a level that provides maximum therapeutic benefit. There are three main categories of controlled release drug delivery systems: intravenous, transdermal, and oral systems. The oral route has certain disadvantages: poor absorption, drug degradation, and bioavailability. Thus the transdermal drug delivery is an especially attractive alternative, because it is usually easy to apply, safe, and painless (Chansai *et al.*, 2009).

There are three primary mechanisms by which active agents can be released from a delivery system: the diffusion, the degradation, and the swelling followed by the diffusion. These mechanisms may occur in a given drug release system.

Effect of environment is considered to affect the DDS. Drug is incapable of releasing until it is placed in an appropriate biological environment such as pH, ionic concentration, and electrical strength. Most of the materials used in swelling controlled release system are based on hydrogels: they are polymers that can swell without dissolving when placed in water or other biological fluids and a diffusion of a drug occurs passing through the polymer that forms the controlled release. Figure 4 shows the controlled drug release under environment stimuli.

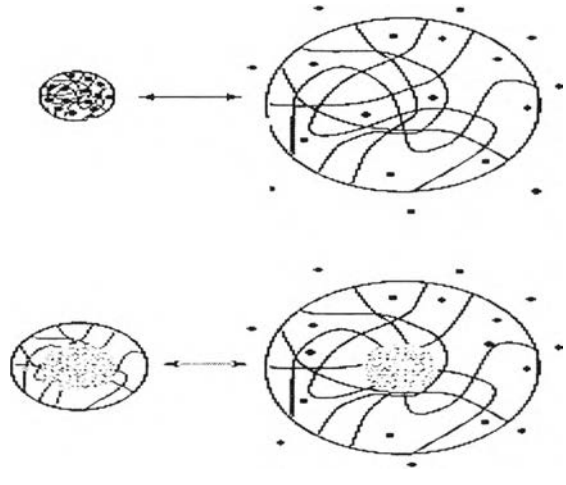

**Figure 2.4** Drug delivery from environmentally sensitive release systems.

Iseki *et al.* (1993) evaluated the efficiency of a PPy membrane as a device for drug delivery using model compounds, which in an aqueous solution produced anions with therapeutic activity. The anions chosen were salicylate, nicoside and naproxen. These anions had an aromatic structure and are of medium size. The delivery of anions from the membrane was followed by using an electrochemical quartz crystal microbalance (EQCM) as well as high pressure liquid chromatography (HPLC) as an analytical tool.

Gudeman and Peppas (1995) prepared interpenetrating networks of poly(vinyl alcohol), PVA, and poly(acrylic acid), PAA. Studying the equilibrium

swelling showed that the molecular weight between crosslink varied from 270 to 40,000 and the mesh size from 19 to 710 Å. The swelling ratio increased with decreasing the ionic strength of the swelling medium. Moreover, they investigated the permeation of solutes of various sizes including urea, guaiacol glyceryl ether, L-tryptophan, vitamin $B_{12}$ and selected dextrans as a function of pH and membrane mesh size. The diffusion coefficients of L-tryptophan and urea were smaller at a pH of 3 than at a pH 6. For FTIC-dextran and vitamin $B_{12}$, dextran permeation was rejected while the smaller solute was transported through the membrane.

Peppas and Wright (1996) studied the effect of ionization on solute diffusion at pH 3 and pH 6 from interpenetrating polymeric networks of PVA and PAA. The ionic strength and temperature were kept constant at 0.2 N and 37 °C, respectively. They found that the swelling increased as the pH increased. They also indicated that as the percentage of PAA increased in these membranes, the equilibrium swelling ratio increased. After that, the mesh size increased with decreasing the crosslinking ratio. Diffusion of theophylline, vitamin $B_{12}$, and myoglobin were determined. The vitamin $B_{12}$ permeation was greater at pH 6 at which the hydrogel was expanded and the mesh size was greater. The permeation of theophylline was greater at pH 6, although the membrane and theophylline were ionized. Myoglobin permeated through the membranes at pH 6 and contained higher amounts of PAA (75% and 100%) at a linear rate.

Hepel and Mahdavi (1997) used a composite PPy film as an ion gate membrane for the potential controlled release of a cationic drug, chlorpromazine. The characterization of the polymer films has been obtained by in situ monitoring of the mass change by a quartz crystal microbalance in conjunction with cyclic voltammetry. The electrochemical quartz crystal microbalance (EQCM) with its excellent sensitivity allowed direct measurement of the amount of the drug released when the potential of the film was changed. The release of a neuroleptic drug, chlorpromazine (CPZ), from a composite PPy/melanin film upon electrical stimulation had been studied.

Peppas and Wright (1998) prepared PVA, PAA hydrogels, and their interpenetrating networks (IPNs) by using glutaraldehyde and ethylene glycol dimethacrylate as crosslinking agents. The molecular weight between crosslinks was

found to be greater than the theoretical values due to the short reaction times of the polymers. The mesh size of the networks was greater at pH 6. Drug diffusion was studied as a function of pH, mesh size, and PAA content. The results indicated that for vitamin $B_{12}$, a neutral solute with mol wt. = 1,355, permeation was greater at pH 6 at which the hydrogel expanded and the mesh size was greater. The permeation of theophylline, mol. wt. = 180 with $pK_a$ of 8.6, was greater at pH 6, although the hydrogel and theophylline were ionized. Myoglobin, mol wt. = 17,200 with pKa of 7.0, did not permeate through the hydrogels at pH 3 but the permeation of myoglobin occurred at pH 6. Myoglobin permeated through the hydrogels that contained higher amounts of PAA (75 and 100%). ATR-FTIR was used to confirm the polymer/drug interactions by showing a shift in the carbonyl region of the spectra.

Ramanathana *et al.* (2001) studied the use of chitosan gels as matrices for electrically modulated drug delivery. Chitosan gels were prepared by the acetylation of chitosan and subsequently hydrated. In the electrification studies, gel mass variation, surface pH changes, and later, release-time profiles for neutral (hydrocortisone), anionic (benzoic acid), and cationic (lidocaine hydrochloride) drug molecules from hydrated chitosan gels were monitored in response to different milliamperages of current as a function of time. Hydrated gels had very similar microviscosity while exhibiting differences in the gel strength, resulted which were not inconsistent as they pertained to different aspects of the gel. The cumulative gel mass loss and rate of gel mass loss increased with an increase in the milliamperage (mA) of the applied current.

Thanpitcha *et al.* (2006) studied films consisting of a blend of a chitosan hydrogel and a conductive polymer. Polyaniline (PANI) were prepared and characterized for their electrical and mechanical properties. PANI in emeraldine base (EB) form was dispersed in chitosan solution and blend films were obtained by solution casting. The PANI particles in the blend films were then doped with HCl where we observed reductions in the film tensile strength and Young's modulus by about 30%, but the films electrical conductivity increased by 6 orders of magnitude. The highest electrical conductivity of the blend films was of the order $10^{-4}$ S/cm. The electrical and mechanical properties of the films varied with polyaniline content, acid dopant type, and acid dopant concentration and doping time.

Juntanon *et al.* (2008) investigated a controlled drug delivery from PVA hydrogel as the matrix/carrier by applied electrical stimuli. The drug-loaded PVA hydrogel were prepared by a solution-casting using sulfosalicylic acid as a model drug and glutaraldehyde as the crosslinking agent. The diffusion coefficients were measured as functions of crosslinking ratio, the mesh size, electric field strength, and the electrode polarity. For the effect of crosslinking ratio, the diffusion coefficient of the drug from PVA hydrogel increased with decreasing crosslinking ratio, for the effect of electric field strength, the diffusion coefficient of drug from hydrogel increased with increasing electric field strength. For the effect of electrode polarity, the diffusion coefficient of drug under cathode was apparently higher than those under anode and under no current.

Mohammad and Mudassir (2008) synthesized cross-linked vinyl acetate-co-acrylic acid (VAC-co-AA) hydrogels by using N,N,methylene bisacrylamide (MBAAm) as a cross-linking agent. Different ratios of 90:10, 70:30, 50:50, 30:70, and 10:90 of VAC-co-AA were synthesized. All of the compositions were crosslinked using 0.15, 0.30, 0.45, and 0.60 mol percent MBAAm. In addition to the above, these hydrogels were loaded with 2%, 8% and 14% w/v aspirin solutions, keeping the monomeric composition and degree of crosslinking constant. These pH-sensitive gels responded to small changes of pH to a much sharper extent than other pH-sensitive gels. Hydrogels with high contents of AA, up to 50 mol percent, showed more drug release than those gels with a low content of AA. However, the drug release was not significantly affected by changing the degree of cross-linking.

Chanisai *et al.* (2009) prepared a conductive polymer–hydrogel blend between sulfosalicylic acid-doped PPy and poly(acrylic acid) (PAA) as a carrier/matrix for the transdermal drug delivery under applied electrical field. The blend was prepared by a solution casting with ethylene glycoldimethacrylate (EGDMA) as the crosslinking agent. The effects of crosslinking ratio and electric field strength on the diffusion of the drug from PAA and PPy/PAA hydrogels were investigated using a modified Franz-diffusion cell. The drug diffusion coefficient decreased with increasing drug size/mesh size ratio, irrespective of the presence of the conductive polymer as the drug carrier. The diffusion coefficient, at the applied

electric field of 1.0 V, became larger by an order of magnitude relative to those without the electric field.

Niamlang *et al.* (2009) compared the controlled release of salicylic acid as model drug from salicylic acid-loaded polyacrylamide hydrogels (SA-loaded PAAM), and salicylic acid-doped poly(phenylene vinylene)/polyacrylamide hydrogels (SA-doped PPV/PAAM). Without an electric field, the diffusion of SA from the SA-doped PPV/PAAM was delayed in the first 3 h due to the ionic interaction between the anionic drug (SA anion) and the PPV. The $D_{app}$ of the SA-doped PPV/PAAM was higher than that of the SA-loaded PAAM, and the former increased with increasing electric field strength that apparently obeyed the scaling behavior: $D_{app}/D_0$ = (drug size/pore size)$^m$. The SA-loaded PAAM and SA-doped PPV/PAAM showed the scaling exponent m equal to 0.50 at 1 V, respectively. However, the drug release rate depended on cross-inking density, electric field strength, drug size, hydrogel matrix mesh size, drug-matrix interaction, and the presence of a conductive polymer.

Islam *et al.* (2011) developed enteric coating from chitosan (CS) and PVA. Solutions of CS and PVA (5:1 mol ratio) were mixed and selectively crosslinked with tetraethoxysilane. FTIR confirmed the presence of the incorporated components and the existence of siloxane linkages between CS and PVA. The crosslinking percentage and thermal stability increased with increasing amount of crosslinker. All hydrogels showed low swelling in acidic and basic pH media, whereas maximum swelling was exhibited at neutral pH. This pH sensitivity of the hydrogel has been exploited as enteric coating for commercial aspirin tablets. The dissolution test of enteric-coated aspirin tablet in simulated gastric fluid (pH 1.2) showed 7.11% aspirin release over a period of 2 h, whereas a sustained release of remaining aspirin (83.25%) was observed in simulated intestinal fluid (pH 6.8).

Lin *et al.* (2012) prepared poly(2-hydroxyethyl acrylate) (PHEA)/silica composites containing aspirin as a model drug were prepared, and their drug release behaviors were tested. The results showed the silica particles were well dispersed in PHEA hydrogels. The in vitro drug release test revealed that the release rate of aspirin decreased with the increasing content of silica. The drug release behaviors were analyzed by employing the power law, which showed that the release profiles

were governed either by Case II diffusion or by anomalous diffusion. The 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay of rabbit chondrocytes revealed that adding silica can improve the biocompatibility of PHEA to some extent.

Paradee *et al.* (2012) synthesized calcium alginate hydrogel (Ca-Alg) using calcium ion as a crosslinking agent and benzoic acid and tannic acid as anionic model drugs and folic acid as cationic model drug under an electric field assisted transdermal drug delivery system. Hydrogel was characterized by its swelling ability and mesh size. The degree of swelling and the mesh size of hydrogel decreased with increasing crosslinking ratios. Moreover, the drug diffusion coefficient also decreased with increasing crosslinking ratios and drug size for all model drugs. The drug diffusion coefficient was precisely controlled by an applied electric field and the electrode polarity depending on the drug charge.

Sittiwong *et al.* (2012) studied the electrically controlled release from PVA hydrogels. PVA hydrogels were prepared by solution casting using glutaraldehyde as a crosslinking agent and benzoic acid (3.31 Å) and sulphanilamide (3.47 Å) as model drugs. The effect of crosslinking ratios was studied. The amount of drug release and the diffusion coefficients of the drugs from the PVA hydrogels increased with decreasing crosslinking ratio, as a larger mesh size was obtained with lower crosslinking ratios. With the application of an electric field, the amount of drug release and the diffusion coefficient increased monotonically with increasing electric field strength, since the resultant electrostatic force drove the ionic drugs from the PVA matrix. The drug size, matrix pore size, electrode polarity, and applied electric field were shown to be influential controlling factors for the drug release rate.