CHAPTER II
LITERATURE REVIEW

2.1 Hydrogels

Polymeric hydrogels have ability to swell in water or in aqueous solutions, and by crosslinking it will not dissolve in the solvent. Hydrogels can shrink or expand in water since it may contain function groups that interact to minute environmental stimuli; for example, pH, solvent, ionic concentration, temperature, light, and electric fields. The hydrogel have weak mechanical properties, so they usually attached to tougher materials. Water in swollen hydrogel can be separated in to three categories, namely bound, interfacial, and free water, depending on the interaction between the polar portion of polymeric material and water. Bound water is strongly associated to polymer chains, interfacial water has weak interaction and free water does not interact with polymer chains. Fig.4 demonstrates three categories of water in a swollen hydrogel.

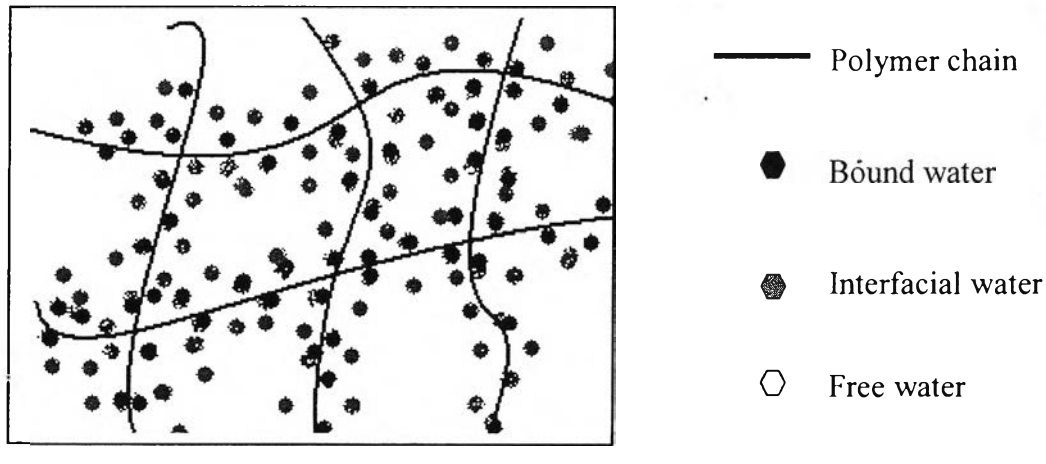


Figure 2.1 Representation of the water structure in hydrogels.

The degree of swelling ratio (Q) can demonstrate by this equation: (2.1).

$$Q = \frac{100(Ws - Wd)}{Wd} \qquad (2.1)$$

where W_s = the weight of swollen sample.

W_d = the weight of dry sample.

The hydrogels have an important feature that is biocompatibility. The biocompatibility is ability to simulate living tissue characteristics such as large water content, low interfacial tension with body fluids, and permeability to metabolites, nutrients and oxygen. Beside hydrogels are used as biomaterials due to many advantages such as

i) The soft, rubbery nature of hydrogels minimizes mechanical and frictional irritation to the surrounding tissues.

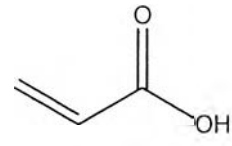
ii) Interfacial tension is low or zero with surrounding biological fluids and tissue.

iii) Hydrogels allow the permeation and the diffusion of low molecular weight metabolites, waste products and salts as do living tissues (Bhat, 2005).

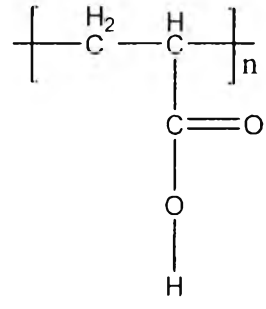
There are several types of hydrogel that have beed studied for controlled drug delivery for example poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, polylactides, poly(ethylene glycol), poly(methacrylic acid).

2.2 Acrylic Acid

Acrylic acid is very brittle and breaks easily, thereby an acrylic acid is cross-linking by using EGDMA as a crosslink agent to from poly(acrylic acid) (PAA) hydrogel. Fig.5 presents the structure of acrylic acid and PAA. Schematic 1 presents the cross-linking of PAA. PAA hydrogels have been more interest in recent years due to it has excellent properties such as the ability to absorb many times, chemical resistivity, and highly biocompatible. PAA is widely used in many applications including diapers, biomedical and biotechnological. Moreover PAA is widely used in pharmaceutical since its pH dependent swelling behavior. The applications of PAA in pharmaceutical are used in the sustained release of drugs. PAA is an environmentally sensitive polymer whose properties can change as functions of pH and ionic strength.



Structure of acrylic acid



Structure of poly(acrylic acid)

Figure 2.2 Structure of acrylic acid and poly(acrylic acid).

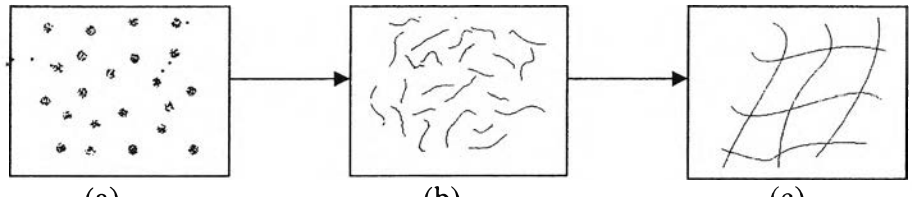


Figure 2.3 Schematic Cross-linking of PAA: (a) monomer of acrylic acid; (b) polymerization of acrylic acid to form poly(acrylic acid); and (c) cross-linking of PAA.

2.3 Conductive Polymers

Conductive polymers are the conjugated polymers that have a backbone of alternating single and double bonds makes them semiconductor. It has special properties that differ from other polymers is electrical conductivity. The electrical conduction properties of conductive polymers are controlled by the addition of small quantity of a foreign molecule (dopant) into the host polymer matrix. There are two types of dopant, n-type (electron donating) and p-type (electron acceptor). In n-type doping, reducing agents added electrons to the conduction band, generating the

negative charges which can delocalize as charge carriers. In p-type doping, oxidizing agents remove electrons from the valence band, generating the positive charges which can delocalize as charge carries. When charge carriers are introduced, the electrical conductivity increases dramatically. Both n-type and p-type dopants have been used to induce an insulator-metal transition in conductive polymers. Because of the thermodynamic stability of intermediates, one of carbocation is greater than one of carbanion result; conductive polymers are usually doped by a p-type dopant (Ruangchuay, 2003). There are many type of conductive polymer for example polyaniline, polypyrrole, Polyacetylene, Polythiophene, Poly(p-phenylene), Polypyridine, and Polyethylenedioxythiophene. The repeating units of some conductive polymers are present in Figure 2.4.

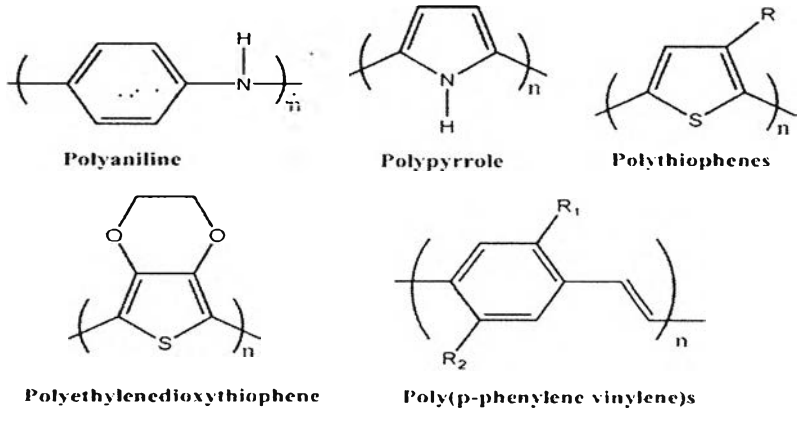


Figure 2.4 The repeating unit of some conductive polymers.

Conductive polymers have many advantages over the metallic or ceramic counterparts such low cost materials, simple fabrication techniques, easy deposition on various substrates, and flexible molecular architectures such as side chain attachments, and modification by charges or neutral particles either in bulk or on the surface (Prissanaroon *et al.*, 2000). There are many applications of conductive polymer including batteries, capacitors, smart windows, light emitting diodes, transistors, photovoltaics, microlithography, corrosion control, conductive adhesives and inks, static dissipation, EMI shielding, radar/microwave absorption, direct plating, electrostatic powder coating, clean room applications, sensors, and drug delivery systems.

Stassen *et al.* (1995) used a conductive polymer, poly-(3-hexylthiophen), as an active separation layer for potential use in drug delivery system and medicamentation. Dopamine was used as the test substance 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 3μm.

Kontturi *et al.* (1998) studied the controlled release of anionic drug, salicylate, naproxen and nicoside, by using the conductive polymer, polypyrrole, as an ion gate membrane. EQCM was used to measure the mass changes and HPLC to determine the release of drugs from the membranes. The stability of the Ppy membrane was found to be good in chloride solutions. 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 an electrochemical quartz crystal microbalance (EQCM) and prepared polypyrrole ion-gate membranes by electrochemical polymerization. When a potential below about 800 mV, polymerization occurred slowly and the structure of membrane was so tight; big anion, TOS^-, was difficult to diffuse. At potential above 900 mV, the membrane had more open structure so the TOS^- ion was easy to move.

Release of anion during reduction of the polypyrrole should undergo at pH value below about 7. There were no significant effects of temperature and permittivity of the solution on ion exchange property of polypyrrole membrane found. The impendent measurements confirmed that ion transport when the membrane was in its charged state and in the reduced state the membrane was an insulator and almost no ion transport occurred.

Petitjean *et al.* (2005) studied the electrochemical oxidation of pyrrole with sodium salicylate as an electrolyte which maked it possible to deposit polypyrrole (PPy) films on oxidizable metals such as zinc. XPS and in situ electrochemical quartz crystal microbalance (EQCM) experiments demonstrated that the passivation of zinc was not due to the formation of a thick insulating layer on the electrode but a very thin composite passivating zinc salicylate layer was formed prior to pyrrole electropolymerization and prevents zinc dissolution. At -0.9 V, pyrrole was present in the inner part of the passivation layer, while at potentials above 0.5 V the formation of conductive passed through the insulating porous layer.

Martins *et al.* (2006) carried out an electrochemical oxidation of polypyrrole with four different neutral or acidic aqueous electrolytes: oxalic acid, sodium oxalate, sodium/potassium tartrate and sodium salicylate. The polypyrrole depositions and film characteristics were compared. From infrared reflexion absorption spectroscopy (IRRAS) in oxalic acid medium, the presence of Cu(I) oxalate was evidenced as the only passivating agent. The weak transmission intensities of the spectra obtained with samples polarized in oxalate and tartrate media suggested thinner layers thus not fully identified, and the salicylate medium was the only one for which one can be distinguished successively the formation of the thin layers consisitng of copper (II) ions complexed by the salicylate anion. They found that sodium salicylate was the most efficient in terms of metal dissolution and potential deposition under galvanostatic conditions at high and low current density, and the qualitative faradic yield. The tartrate medium was also suitable for galvanostatic deposition at high and low current density but with a lower faradic yield (50%) whereas oxalic and oxalate media were suitable for PPy deposition at low current densities or under potentiodynamic conditions.

Wadhwa *et al.* (2006) investigated the drug delivery of an anti-flammatory drug, dexamethasone (Dex), from polypyrrole coating on the electrode sites. The drug was incorporated in Ppy via electropolymerization of pyrrole and released in PBS using cyclic voltammetry (CV). From AFM, the film morphology appears rougher at higher charge density and higher drug release. They were able to release 0.5 $\mu g/cm^2$ Dex in 1 CV cycle and 16 $\mu g/cm^2$ Dex after 30 CV cycles from a 50 nm thick Ppy/Dex film.

Arbizzani *et al.* (2007) investigated the properties of Ppy for its application in drug-eluting membrane. Ppy was electrosynthesized on a metal surface using anionic drugs, salicylate and naproxene, as electrolyte and toluenesulfonate as a counterion. EQCM was used to evaluate the increase of mass during electropolymerization and to investigate the motion of anions and cations across the polymer film during discharge in order to estimate the amount of drug. The amount of drug was controlled by the charge involved in the electropolymerization process. The amount of TS^- still present in the polymer after its discharge was 70% of that initially inserted during electrosynthesis. Whereas 50% of the Sa^- and 85% of Np^- inserted during electrosynthesis remained inside the polymer after its discharge. The drug remained entrapped in the polymer during its discharge and can be released over 7-30 days and found that Sa^- was eluted fastest but Np^- was eluted most.

Gade *et al.* (2007) synthesized the conducting polymer Ppy by 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, and investigated influence of electrochemical process parameters such as monomer and electrolyte concentrations, current density, pH of the electrolyte, and type of electrolyte during polymerization of Ppy. They indicated that the conductivity depends on the anion present in the electrolytes which followed the order NO_3^- > Cl^- > COO^-, and the plateau potential increases there was a decrease 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.

Small *et al.* (1995) prepared and characterized conductive polymer-hydrogel composites. The responsive properties of these materials were investigated. They found that a continuous open porous structure was maintained during the polymerization. In the cylindrical gel-cell, even after extensive polymerization times conducting polymer was not deposited at the gel-solution interface due to the pH differential, between in the gel (near the working electrode) and outside the gel, would prevent polymerisation at the gel-electrolyte interface. Hydroxide generated at the auxiliary or some other by-product inhibited the electropolymerization. The thin gel-cell was used as a membrane with excellent electroactivity. The efficiency of controlled release decreased when the size of hydrophobicity, calcon, increased.

2.4 Polypyrrole

Polypyrrole (PPy) is one of conductive polymer which is of great attention since it exhibits high electron conductivity, good environmental stability, easy to synthesis, and it process excellent thermal and electron properties. However PPy has low selectivity, poor mechanical property, and inefficient solubility. Ppy can often be used for biosensors, gas sensors, microactuators, antielectrostatic coatings, solid electrolytic capacitor, electrochromic windows, displays, packaging, polymeric batteries, electronic devices and functional membranes. Moreover Ppy based polymers can be used to load drugs, biomolecules, and in biosensor applications (Gade *et al.*, 2007).

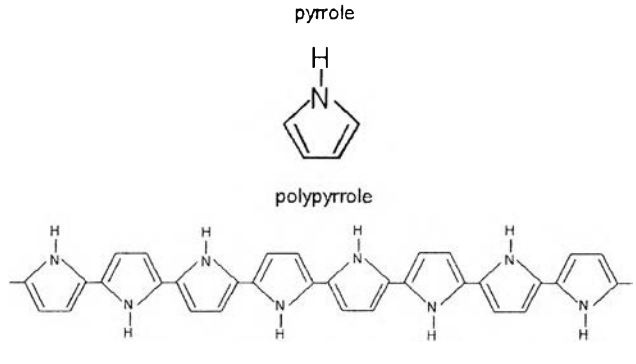


Figure 2.5 Structure of pyrrole and polypyrrole.

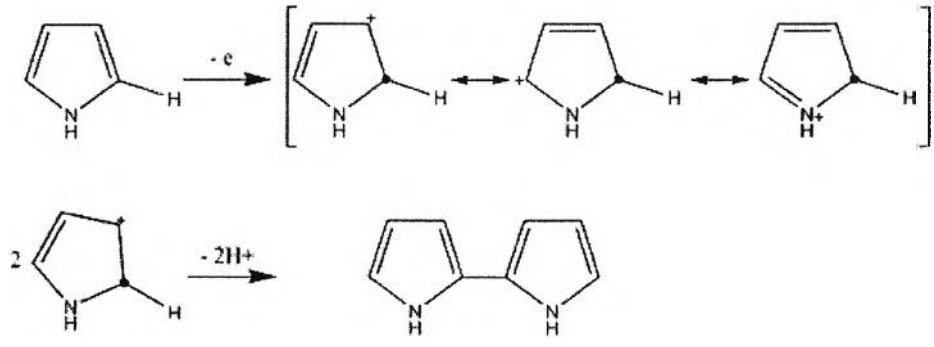


Figure 2.6 Mechanism of polymerization, shown as the example of pyrrole oxidation.

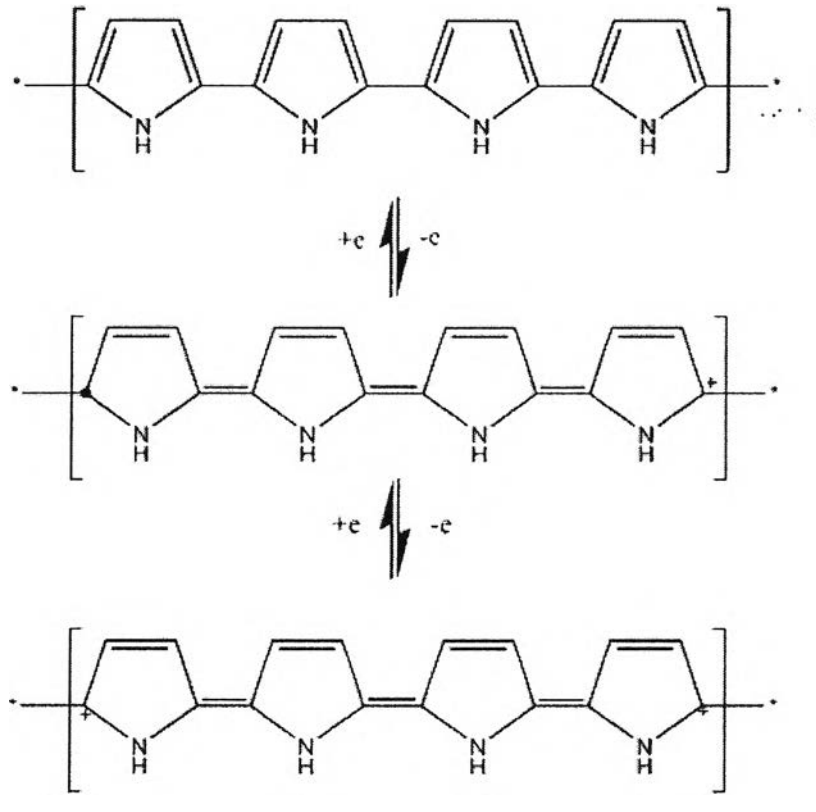


Figure 2.7 Polarons and bipolarons of conducting polymers. The charge is compensated by counterions from the electrolyte.

Normally Ppy is polymerized by either an electrochemical or chemical method. Ppy that is synthesized either chemically or electrochemically is insoluble due to the strong inter- and intra-molecular interactions and cross-linking (Kings *et al.*, 1993). Thus the insoluble and infusible nature of Ppy restricts its applications and processing. The incorporation of a large-sized protonic acid as a dopant into the polymer reduces the inter- and intra-molecular interactions, thereby increasing solubility (Lim *et al.*, 1999). There are two doping structures of Ppy,(1) oxidized conjugated chain doped with counter-anion and (2) a proton acid doping structure.

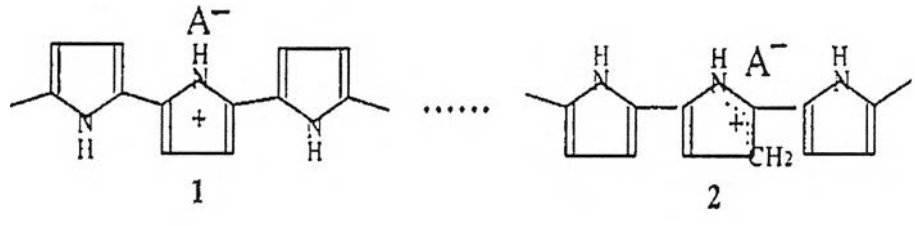


Figure 2.8 Show two doping structures of Ppy (Li and He, 1998).

Lee *et al.* (1995) synthesized polypyrrole by a chemical polymerization using dodecylbenzene sulfonic acid as the dopant and ammonium persulfate as the oxidant. Synthesized Ppy became soluble in the doped state in m-cresol and conditionally soluble in the weakly poor solvents. The spectroscopy of FT-Raman scattering and UV-VIS light absorption indicated that the chemical structure of the polymer was identical to that of the polymer formed electrochemically. The intrinsic viscosity of the polymer in m-cresol was 0.17 dl/g. The solution of the polymer in chloroform was cast to a stiff film with a very smooth surface and the electrical conductivity was 5 S/cm. The elastic modulus, elongation at break, and tensile strength were 1945 MPa, 0.9 %, and 17 MPa, respectively. The electrochemical reactivity was sustained after 150 cycles of cyclic voltammetry.

Appel *et al.* (1996) reported a method to deposit thin films of conductive polypyrrole powder. Polypyrrole tosylate was synthesized by a chemical oxidation of pyrrole with ammoniumpersulfate in aqueous solution. They used several methods of film deposition to obtain smooth and highly conducting polypyrrole films. The

concentration of the oxidant had strong influence on the conductivity and when the reaction time was short, the best results were obtained. Films deposition by dropping method was thick and porous film, but brittle. When compared between spraying and dropping method, spraying film could reduce the deposition rate, a thinner film, generated fewer cracks and a sprayed film showed only 10-15% of the conductivity. By spin coating smooth films with thickness of some 100 nm were obtained. Very thin films could produce by exposing an oxidant/dopant solution to pyrrole porous and show a conductivity of 6.1 S/cm.

Li and He (1998) investigated the effect of electrolyte concentration of polymerization solution and temperature on the two doping structures: (1) oxidized conjugated chain doped with counter-anion; and (2) proton acid doping structure, of polypyrrole nitrate film via elemental analysis and cyclic voltammetry. They found that the doping degree of (1) increased when the Ppy(NO_3^-) film was prepared in the solution with higher $NaNO_3$ concentration, higher values of conductivity and tensile strength, and a decrease in temperature. But structure (2) was easily formed in low electrolyte concentration and at higher temperature.

Lim *et al.* (1999) studied the changes that occurred during the in situ thermal deposition of aluminium (Al) on the chemically synthesized polypyrrole (Ppy) film in its salt and partially undoped/deprotonated forms by using X-ray photoelectron spectroscopy (XPS). They found that the Al atoms introduced during the evaporation process reacted preferentially with the dodecylbenzene sulfonic acid dopant to form an aluminium salt. It was also observed that in response to the Al deposition process, adsorbed oxygen atoms from the bulk of the films diffused to the surface, resulting in the increase in surface oxygen concentration. The formation of the N-π-AlO_x complex disrupted the π-electron conjugation in the imine units and reduced them to a state equivalent to that of the amine structure, causing the observed decrease in the intrinsic oxidation state of the polymer.

Kang and Geckeler (2000) investigated the effect of the preparation technique and a polymer additive on the electrical conductivity of PPY when ferric chloride was used as an oxidant in the aqueous phase. They found that the electrical conductivity of chemically prepared polypyrrole in aqueous solution was strongly dependent on the preparation technique and polymer additive. The conductivity of

polypyrrole prepared in the presence of poly(ethylene glycol) (PEG) additive, (PPY-H), was found to be higher than those of polypyrrole synthesized without additive. Conductivities increased in the follow order: PPY-H > PPY-S > PPY-F > PPY.

Prissanaroon *et al.* (2000) synthesized and characterized of polypyrrole which was soluble in *m*-cresol. Ammonium persulfate (APS) was used as an oxidant. Dodecylbenzene sulfonic acid (DBSA) was used as the dopant. They investigated the effect of DBSA concentration on the electrical conductivity of Ppy thin films in N_2 and SO_2 atmospheres. Ppy films doped with DBSA can be used to detect small amounts of SO_2 in SO_2 –N_2 mixtures. The gas sensitivity of a film give doping level increased with SO_2 concentration. From SEM, they investigated the effect of doping level on the morphology of Ppy and found that increasing the dopant level, the morphology of the conductive polymer changed from having typical three dimensional random coils, granular structures to rigid rod-like, fibrillar structures.

Song *et al.* (2000) studied the solvent effects on the properties of the soluble polypyrrole (PPy) doped with DBSA and investigated solubility and electronic structures of the doped Ppy in various organic solvents. Chemically synthesized Ppy having electrical conductivity 1.0 S/cm with DBSA dopant was dissolved in organic polar solvents and cast into a film showed reduced conductivity of 10^{-2} S/cm. The Ppy doped with DBSA could dissolve in weakly polar solvents and showed no change in the conductivity when cast into films. The more oxidant was used, the higher electrical conductivity and the higher yield were obtained. But, the solubility was reduced if the oxidant ratio, oxidant/monomer mole ratio, was too high. Raman spectra suggested that the Ppy–DBSA film from NMP contained polarons but that from DBSA/chloroform did mainly bipolarons. The size of the micelle was strongly influenced by the molecular weight of the polymer due to the hydrodynamic radius of the Ppy–DBSA micelle increased with an increase of the electrical conductivity of the powder that was related to the molecular weight of Ppy.

Ruangchuay *et al.* (2004) studied effects of dopant anions on polypyrroel to be used as a chemical sensor to detect acetone vapor. The specific conducyivity depended on type of dopants existing in Ppy. The dopants which provided Ppy with higher specific conductivity, higher order aggregation, higher proportions of N_2, especially bipolaron and lower proportion of imine-like nitrogen defect could

improve the sensitivity to the acetone vapor. From the study on effect of dopant anions on the response of Ppys toward acetone vapor, Ppy/A and Ppy/B were found to be the most promising materials for sensing acetone whereas Ppy/AB had the lowest response toward acetone vapor. From the investigation of interaction between acetone vapor and Ppy, after immersing in acetone liquid for 30 min the peak changed due to acetone destroyed the dispersion force between aromatic pyrrole units and increased the disorder section in Ppy which hindered the electron mobility and hence decreased the specific conductivity of PPy.

Song *et al.* (2004) studied the polymerization yield, solubility and conductivity of soluble polypyrrole (Ppy), chemically synthesized with alkylbenzenesulfonic acid (ABSA) dopants. Moreover, they investigated the molecular size effect of dopants by spectroscopic study and X-ray analysis. When the monomer-to-oxidant ratio, [Mo]/[Ox], was ranged from 2.5 to 15 for Ppy doped with DBSA. The lower conductivity at low oxidant concentration might be associated with the lower molecular weight. The polymerization yield increased with longer alkyl chain length of the dopants. The doping level of Ppy powders increased with alkyl chain length. The UV/VIS/NIR results showed that the higher conductivity resulted from shorter chains length of Ppy and high concentration of bipolaron. The XRD results showed that only DBSA induced a layered and ordered structure, where the long alkyl chain in DBSA molecules worked as a spacer between polymer chains.

Carrasco *et al.* (2006) determined chemically synthesized polypyrroles of low (σ < 75 S/cm), medium (75 < σ < 200 S/cm) and high (σ > 200 S/cm) electrical conductivity (σ) with the same dopant and degree of doping by using Wide Angle X-ray Scattering (WAXS). WAXS spectra for Ppy of medium and high conductivity showed a weak peak at 2θ = 10–11°. WAXS indicated that the structure of Ppy doped with common inorganic counterions such as Cl^-, ClO_4^-, BF_4^- and PF_6^- are essentially amorphous. From the FTIR spectra, they showed that the polymerization and storage conditions have not produced significant oxidative degradation of the backbone of the Ppy of low, medium, and high conductivity.

2.5 Transdermal Drug Delivery System (TDDS)

Drug delivery system is the control of the drug into a body at a desired target with a suitable amount of drug for the best treatment. A drug delivery system has two functions. The first function is the introducing of the drug to a particular part of the body and the second function is controlling the drug release. The control-released drug delivery is necessary because if the drug concentration is very high, it contributes to adverse side effects. And if the drug concentration is too low, it provides a therapeutic benefit. The drugs releasing is desired at a constant rate, thereby it needs to maintain drug concentration within the therapeutic range and eliminating for frequent dosages. Due to the important property of conductive polymer is controlling the ionic transport of counterions (dopants) in and out of the membranes by oxidation or reduction so the drug delivery system with conducting polymers can control releasing rate. The mechanism of drug delivery is as follows: water diffuses into the membrane or matrix, the drug dissolves, and last the dissolved drug diffuses out of the polymer. There are three main categories of controlled-release drug delivery systems; intravenous, transdermal, and oral systems. Transdermal drug delivery has many important advantages over oral drug delivery. For the oral drug delivery, some drugs first pass metabolism in the intestinal tract or in the liver, thereby the drugs may loss some activity or may affect liver toxic metabolites.

Transdermal drug delivery system (TDDs) has gain attention in recent year. TDDs is applied to skin to allow a drug pass through skin to impart systemic or local therapeutic effect. The factors to control iontophoretic drug delivery across the skin are current density and donor drug concentration; both of which are directly related to the drug flux. TDDs has many advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time, decreasing side effects, composition relatively invariant in use, can be fabricated in a desired size and shape, can control site and using time, easy to be used, a decrease in gastrointestinal effect that occurs during chronic treatment using conventional oral

route, and improved compliance. The rate of release depends on the polymer composition, the drug diffusion, and the thickness of membrane.

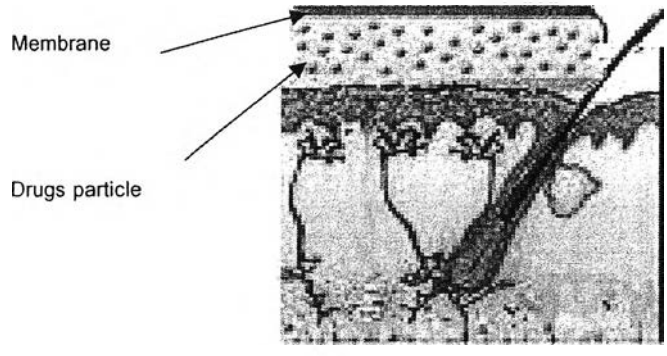


Figure 2.9 Transdermal drug delivery on the skin.

Gudeman and Peppas (1995) synthesized interpenetrating networks of poly(vinyl alcohol) and poly(acrylic acid). Studying the equilibrium swelling demonstrated 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 a decrease in the ionic strength of the swelling medium. Furthermore, 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. They found that for L-tryptophan and urea, the diffusion coefficient was smaller at a pH of 3 than at a pH 6. For FITC-dextran and vitamin B_{12}, dextran permeation was rejected while the smaller solute was transported through the membrane.

Peppas and Wright (1996) prepared PVA, PAA, and IPN hydrogels to study the effect of ionization on solute diffusion at pH 3 and pH 6. 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. When the cross-linking ratio decreased, the mesh size increased. Diffusion of theophylline, vitamin B12, and myoglobin were determined. The permeation of vitamin B12 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.

Peppas and Wright (1998) prepared hydrogels of PVA, PAA, and their interpenetrating networks (IPNs) and characterized neutral and hydrophilic gels and studied their diffusional properties. The molecular weight between crosslinks was found to be greater than the theoretical values. The mesh size of the networks was greater at pH 6. Furthermore they studied theophylline, vitamin B_{12} and myoglobin diffusion through these hydrogels. For vitamin B12, permeation was greater at pH 6 at which the hydrogel was expanded and the mesh size was greater. The permeation of theophylline with p*K*a of 8.6 was greater at pH 6. Myoglobin with p*K*a of 7.0 did not permeate through the hydrogels at pH 3 but the permeation of myoglobin occured at pH 6. At 75 and 100% PAA containing myoglobin was permeated. ATR-FTIR was used to study the interactions between PAA hydrogel and myoglobin showing a shift in the carbonyl region of the spectra.

Akerman *et. al.* (1999) studied the interaction between the drug and the poly(acrylic acid) grafted poly(vinylidene fluoride) (PAA–PVDF) membranes and drug delivery by using sodium salicylate (anionic), flunitrazepam (neutral), primidone (neutral), desipramine (cationic) and thioridazine (cationic) as model drugs. Furthermore, they evaluated the influence of pH, the ionic strength and the concentration of albumin in the adsorption medium as well as the charge and lipophilicity of a model drug on their adsorption onto PAA–PVDF membranes. Adsorption of all the studied drugs onto the membrane was affected by environmental pH. The model drugs were adsorbed more efficiently at pH $\geq$7.0. The expanded conformation of PAA chains enhanced the adsorption of the drugs onto the membrane. Increasing the ionic strength of the medium retarded the adsorption of the cationic drugs. The drugs were adsorbed onto the membrane while albumin was not adsorbed onto the membrane thus PAA–PVDF membrane may be suitable for separating drugs from proteinaceous substances.

Akerman *et al.* (1999) examined the effect of ionic strength on the drug adsorption onto and release from the PAA-PVDF membrane. It was found that ionic strength of adsorption medium, degree of grafting, and concentration of propanolol-HCl in adsorption medium effect propanolol-HCl adsorption onto the membrane.

The fluxes of small molecules across the membrane decreased as the ionic strength of buffer solution increased. On the other hand, the fluxes of large molecule increased as the ionic strength was elevated. Adsorption of propanolol-HCl on the membrane trend to decreased with increasing ionic strength.

Jaskari *et al.* (2000) studied the properties of the ion-exchange fibers in the transdermal drug delivery. Tacrine, propranolol nadolol and sodium salicylate were used as model cationic and anionic drugs. Drug release from the cation-exchange fiber into a HEPES buffered was dependent on the lipophilicity of the drug. The release rate of hydrophilic nadolol was larger than those of lipophilic tacrine and propranolol. The hydrophilic drug nadolol exhibited the lowest flux, thus it hardly entered the skin. The iontophoretic flux enhancement of sodium salicylate from the fiber was substantial.

Bose *et al.* (2001) observed the electrically assisted transdermal delivery of buprenorphine. Buprenorphine HCl (1mg/ml) in citrate buffer (pH 4.0) was delivered in vitro across skin via iontophoresis at current density of 0.5 mA/cm^2 and silver-silver chloride electrodes. The amount delivered under anode was much higher than that delivered under cathode. The passive transdermal flux of buprenorphine HCl was enhanced by the iontophoresis under anodic polarity.

Sutani *et al.* (2002) prepared copolymerization of a polyampholyte by UV and radiation with anionic monomer, acrylic acid, and using 2-(Dimethylamino)ethyl methacrylate or Methacryloyloxyethyltrimethylammonium chloride as a cationic monomer. The pH responsive swelling behaviour and the pH and electro-responsive drug release functions of polyampholyte were studied. It was demonstrated that a copolymer of cation rich composition swelled at acidic condition, and shrank at alkaline condition. But, an anion rich copolymer showed the opposite behavior. The highest max drug release was 50%, because the drug was occluded into the inner part of polymer and could not be released from the network. The amount of drug release from the copolymer of equimolar anionic and cationic composition was higher than from the anion rich copolymer. The drug release was not controlled by the diffusion mechanism. The drug release can be controlled better in the chemical binding drug.

Gondaliya and Pundarikakshuda (2003) designed and evaluated unilaminate transdermal adhesive matrix systems capable of diffusing bupropion base at a

constant rate over an extended period of time as an alternative route of administration. The epidermal flux increased with increasing concentration of bupropion. The release of drug from the matrices was zero order release kinetics (r^2 = 0.9810 to 0.9960). Proper selection of drug/polymer concentration and the size of the system resulted in the satisfactory drug delivery rate of bupropion.

Elliott *et al.* (2004) studied a crosslinked PAA hydrogel made by a free radical polymerization mechanism and investigated factors controlling the degree of crosslinking and primary cyclization during the network formation. It was found that increasing the amount of water present during the polymerization increased primary cyclization rates, and increased the swelling behavior of the acrylic acid hydrogel. The higher degree of cyclization resulted in a smaller crossinked mesh. When the pH was increased, the degree of primary cyclization decreased; while increasing the ionic strength resulted in an increased cyclization.

Prasad *et al.* (2005) studied iontophoretic method for enhancing the transdermal transport of methotrexate across the skin using hydrogel patches. The crosslinking density was increased while the methotrexate permeation increased. So changing the crosslinking density of hydrogel can be used for controlling the drug permeation. Poly(acrylamide-co-acrylic acid) was synthesized and they observed that there was a decrease in the release of the drug with increasing acrylic acid content due to the interaction of the drug with the monomer. Enhancing permeation of methotrexate was by using a current density of 0.2 mA/cm^2.

Dai *et al.* (2006) prepared and characterized poly(acrylamide-*co*-acrylic acid), P(AAm-*co*-AAc), hydrogel. They studied the effects of monomer, initiator, cross-linker, and the change of environmental temperature on the optical transition of the hydrogel. The hydrogel could swell or collapse with changing temperature resulting in opaque white or transparent appearances. P(AAm-*co*-AAc) hydrogel was transparent at about 37°C, while it was white opaque at low temperature of about 15 °C. A higher polymer concentration in the hydrogel became transparent at higher temperature. A lower density of cross-links gave a smaller elastic retracting force. The hydrogel with higher initiator concentration caused the inhomogeneity within the hydrogel but a lower initiator concentration led to a smooth free radical reaction and a homogeneous hydrogel. The P(AAm-*co*-AAc) hydrogel was applied

in drug controlled release or other actives molecule due to its swelling or collapse property.

Liu *et al.* (2006) evaluated the effect of cross-linking polymerization of acrylic acid in $scCO_2$ in a 20 mL batch reactor and an 800 mL CSTR on polymer properties. From SEM, the morphology of the polymer particles was not affected by cross-linking. Water-soluble and water-insoluble polymers could be produced by adjusting the cross-linker concentration. Viscosity measurements showed that the polymer thickening effect depended on the degree of cross-linking, monomer and initiator. The glass transition temperature was affected by the degree of cross-linking. The monomer conversion decreased when using a cross-linker in the CSTR.

Serra *et al.* (2006) studied the drug transport mechanism and release kinetics from molecularly designed poly(acrylic acid-*g*-ethylene glycol) hydrogels. P(AA-g-EG) hydogels were prepared by free radical solution UV polymerization using ethylene glycol dimethacrylate and the theophylline as a crosslinking agent and a model drug, respectively. The effect of hydrogel crosslinking density on theophylline release kinetics was studied. It is clear that drug release was significantly hindered as the hydrogel crosslinking density was increased. An increase in the molar concentration of croslinking agent EGDMA decreased the molercular weight between crosslinks which in turn resulted in a smaller network mesh size and a less flexible structure.