CHAPTER II
LITERATURE SURVEY

2.1 Conductive Polymers

In 1977, the first electrically conducting organic polymer, doped polyacetylene, was reported, spurring interest in conductive polymers. The common electronic feature of pristine (undoped) conductive polymers is the π-conjugated system formed by the overlap of carbon p_z orbitals and alternating carbon-carbon bond lengths. Figure 2.1 shows the chemical repeating units of the pristine forms of several families of conductive polymers. The conductivities of the pristine polymers are transformed from insulating values to metallic values through the process of doping, in which the electrical conductivity increase with the doping level. Both *n*-type (electron donating) and *p*-type (electron accepting) dopants have been utilized to induce an insulator-metal transition in electronic polymers. The doping procedures differ from conventional ion implantation used for semiconductors. The doping process for polymers is carried out electrochemically by exposing the films to vapors or solutions of the dopants. The dopant atoms are positioned interstitially between chains, and donate charges to or accept charges from the polymer backbone. The polymer backbone and dopant ions form new three-dimensional structures (Sim *et al.*, 2001).

Conductive polymers can offer a variety of advantages for electrorheological, ER, systems, such as better thermal stability, insolubility, and more controllable viscosity. Suspensions of conductive polymers exhibit intrinsic ER properties without the necessity to introduce other additives. The polarization is induced via electron movement through polymer backbone under an electric field. The conjugated π-electron system in conductive polymers displays unusual electronic properties, including high electron affinities, and low ionization potentials. The local electron distribution of particles induces the ER effect under the application of electric field. The well known examples of conductive polymers are

polyacetylene, polyaniline, polypyrrole, polythiophene, and poly(p-phenylene vinylene).

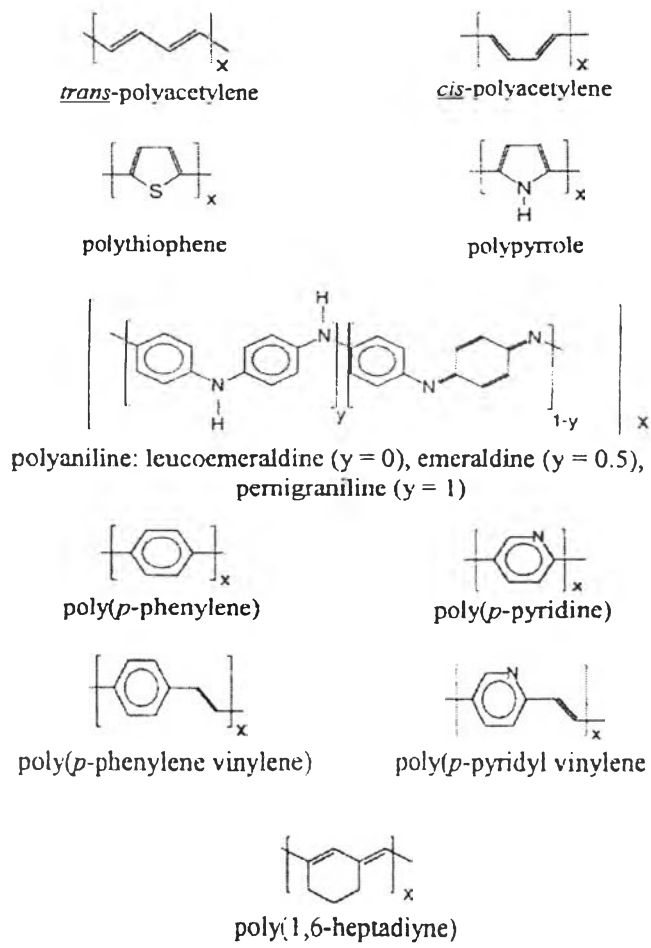


Figure 2.1 Repeating units of several conductive polymers.

2.1.1 Conduction Mechanism

Conduction is the transport of charge from one point to the other and is governed by the movement of charge carriers through a specimen. In general, the conductivity (σ) can be described by the following equation (Chandrasekhar, 1999; Deependra *et al.*, 2004):

$$\sigma = |q| \cdot n \cdot \mu \ [\text{S/cm}] \qquad (2.1)$$

where q is the charge carried by the carrier [A.s], n is the number of charge carriers [cm^{-3}], and μ the mobility of the charge carriers [$cm^2.V^{-1}.s^{-1}$].

Conduction in solids can be described with the widely accepted band model (Blythe and Bloor, 2005). In this model two new molecular orbitals arise when two atoms, both with half filled orbitals, are brought close enough to each other for the orbitals to overlap (cf. molecular orbital theory). The energy-difference (E_g) between the newly formed orbitals is determined by the degree of the overlap between the constituting orbitals. As the degree of overlap is different for every pair of orbitals, the low-energy band or the valence band (VB), and the high-energy band or the conduction band (CB), are formed (Figure 2.2).

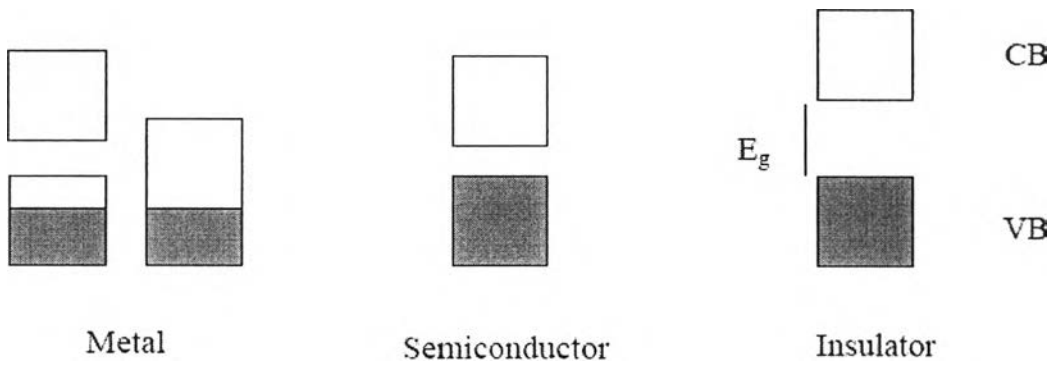


Figure 2.2 Schematic representation of the band structure of a metal, a semiconductor, and an insulator. (E_g is the energy gap between the valence band, VB, and the conduction band, CB).

The extent of occupation of the energy bands and the energy gap between them determine the electrical conductivity of a material. Metals are characterized by either a partially filled VB or an overlap between the VB and the CB. This implies a complete freedom of movement for the charge carriers under the influence of an applied field (Equation 2.1, $\mu \rightarrow \infty$). In semiconductors and insulators, the VB is completely filled (Equation 2.1, $\mu = 0$) and the CB is empty (Equation 1.1, $n = 0$). Therefore, conduction can only take place when charge carriers are promoted from the VB to the CB. In insulators, the energy gap is too large for

charge carriers to be thermally excited, whereas for semiconductors excitation is possible. Because polymer molecules do not extend over the full specimen, charge carriers have to move along the extended π-system of the conjugated backbone (intrachain conductivity) as well as between the individual molecules (interchain conductivity). The measured macroscopic electrical conductivity is a superposition of these microscopic conduction mechanisms.

The majority of theoretical considerations are based on polyacetylene (Figure 2.3), being the simplest conjugated polymer. In *trans*-polyacetylene two energetically equivalent resonance structures are possible (two-fold degeneration). At the conversion points of these structures unpaired electrons are present; they are called solitons. This conversion point is actually spread out over several bonds.

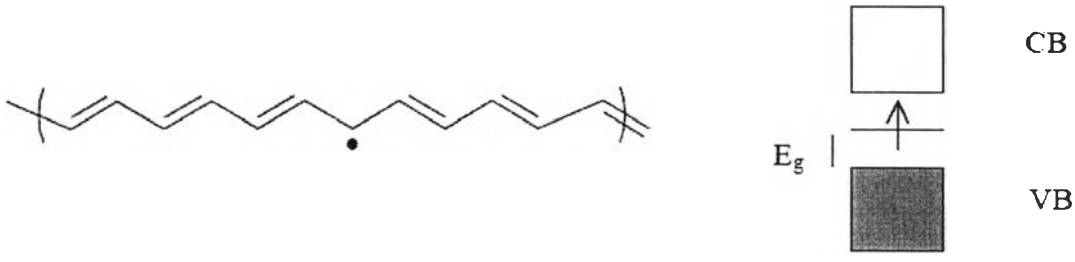


Figure 2.3 Soliton in trans-polyacetylene (left) and electronic state induced between the VB and CB by the soliton (right).

Solitons introduce a localised electronic state in the middle of the energy gap between the VB and the CB of polyacetylene. As this reduces the energy gap for charge carriers, conductivity is facilitated. Solitons are chargeless, but spin carrying (i.e., neutral radicals). An interesting feature of solitons in *trans*-polyacetylene is that, because of the degenerate ground state, they can move along the chain without the need to overcome an energy barrier. In fact, this is why they are called solitons: they have the same properties as a solitary wave. For *cis*-polyacetylene the two resonance structures are non-degenerate and therefore the movement of charge carriers along the backbone is energy consuming. This is

shown by the lower conductivity of *cis*-polyacetylene compared to *trans*-polyacetylene (10^{-11} and 10^{-6} S/cm, respectively). Other conjugated polymers such as poly(p-phenylene vinylene) (PPV) also do not have a degenerate ground state. Still, different resonance structures can be present (cf. the benzoid and quinoid structures of PPV) and unpaired electrons are formed at the conversion points. These electrons polarise the local environment, which then relaxes into a new equilibrium position. This induces two electronic states in the band gap, again facilitating conductivity. The combination of a charge carrier and its distorted environment is called a polaron. The chemical equivalent is a charged radical.

2.2 Doping

The number of naturally occurring solitons and polarons in conducting polymers is not sufficient to render them highly conducting (e.g., 10^{-6} S/cm for *trans*-polyacetylene). Charge carriers can be generated by the oxidation or the reduction of the polymer. This process is called doping, after the similar treatments in metals. The mechanism of doping in polymers however is different from that in metals. In doped metals, non-equivalent dopant atoms replace the metal atoms. Depending on the valence of the dopant, either holes (lower valence) or electrons (higher valence) are generated, which can act as charge carrier. Upon doping of polymers, charge is transferred from the dopant to the polymer. In the oxidation of the polymer (electrons from polymer to dopant) results in a hole-conducting polymer (p-type), In the reduction, an electron-conducting polymer (n-type) is formed (electrons from dopant to polymer). In order to maintain charge neutrality, counter-ions are also incorporated. Confusingly, these counter-ions are sometimes called dopant ions. Counter-ions lower the mobility of the charge carriers by their interaction with the charge carriers on the conjugated polymer (pinning effect). This pinning effect is less when the size and the degree of charge delocalisation on the counter-ion is larger. Furthermore, the stability of the conductivity shows a positive relation with the size of the counter-ion, whereas the diffusion rate of the counter-ion into the doped layer shows a negative relation with size (Kumar and Sharma, 1998).

Doping of polyacetylene results in the formation of new neutral solitons and the charging of both newly formed and already existing solitons. The chemical equivalents are carbocations or -anions, radical cations or anions (polarons), and carbodianions or –dications (bipolarons). Doping of conductive polymers other than polyacetylene results in the formation of polarons and the further oxidation/reduction of newly formed and already existing polarons. The presence of solitons, polarons, and bipolarons in conjugated polymers has been observed in several studies. The increase in conductivity upon doping can be as high as 14 orders of magnitude for different polymer-dopant combinations (Kumar and Sharma, 1998). Upon doping with n-type dopants, organic anions are formed that are highly unstable towards air and water. Consequently, the conductivity generated by n-type doping is less stable than by p-type doping. Therefore, p-type dopants are more frequently used. Some examples are I_2, AsF_5, $FeCl_3$, nitrosonium salts (e.g., $NOPF_6$) and acids (e.g., H_2SO_4, $HClO_4$).

2.3 Poly(p-phenylene vinylene)

Poly(p-phenylene vinylene) (PPV, or polyphenylene vinylene) is a challenge conducting polymer of the rigid-rod polymer host family (Wessling *et al.*, 1967). PPV is the only polymer of this type that has so far been successfully processed into a highly ordered crystalline thin film. PPV is prepared by thermal processing of a precursor polymer. By careful control of the processing it is possible to influence the structure and morphology of the film. Polyphenylene vinylene is capable of electroluminescence, leading to applications in polymer-based organic light emitting diodes. PPV was used as the emissive layer in the first polymer light-emitting diodes. Devices based on PPV emit yellow-green light, and derivatives of PPV obtained by substitution are often used when light of a different color is required. In the presence of even a small amount of oxygen, singlet oxygen is formed during operation, by energy transfer from the excited polymer molecules to oxygen molecules. These oxygen radicals then attack the structure of the polymer, leading to

its degradation. Special precautions therefore have to be kept during manufacturing of PPV in order to prevent oxygen contamination (Wessling *et al.*, 1967).

Wessling *et al.* (1967) developed the soluble precursor routes to PPV. This process was based upon the aqueous solvent synthesis of poly(p-xylylene-a-dialkylsulfonium halides) from α,α'-bis(dialkyl sulfonium salts), followed by the thermolytic formation of the final conjugated polymer. The charged sulfonium groups solubilize the polymer and are removed during the conversion step. Molecular weights for the polyelectrolyte were in the 10,000 to.1,000,000 range, which could be precipitated or dialyzed to give typical yields of about 20% high molecular fraction.

Sakamoto *et al.* (1991) studied the resonance Raman spectra of sodium-doped poly(*p*-phenylenevinylene) (PPV) and the radical anions and dianions of three model compounds $CH_3(C_6H_4CH{=}CH)_nC_6H_4CH_3$ (PVn, n = 1-3). The Raman spectra of sodium-doped PPV showed marked changes with laser wavelengths used for the Raman excitation. These spectra have been analyzed on the basis of the resonance Raman spectra of the radical anions and dianions of the model compounds, which correspond, respectively, to the negative polarons and the bipolarons in PPV. Three kinds of negative polarons whose lengths were close to PV1, PV2, andPV3, and a bipolaron which was localized in a region close to PV3, existed in a sodium-doped PPV film. Upon prolonged heat treatment of the sodium-doped PPV (290 °C, 12 h), the shortest polaron corresponding to the radical anion of PVl disappeared, probably because it combined with another polaron to form a bipolaron. These results indicate that resonance Raman spectroscopy is a powerful tool for characterizing polarons and bipolarons in conducting polymers.

Sakamoto *et al.* (1991) observed the resonance Raman and infrared spectra of sulfuric-acid-treated poly(*p*-phenylenevinylene) (PPV) on the basis of the resonance Raman spectra of the radical-cation and dication species of the model compounds $CH_3(C_6H_4CH{=}CH)_nC_6H_4CH_3$ (PVn, n = 1-3), which corresponded, respectively, to the positive polarons and the bipolarons in PPV. Sulfuric-acid-treated PPV was considered to contain a considerable amount of positive polarons having a more or less uniform length and a relatively small amount of positive bipolarons. Of

the two electronic absorption bands at 2.25 and 1 .OO eV of sulfuric-acid-treated PPV, the former absorption band was due to the positive polarons, whereas the latter had overlapping components arising from the positive polarons and bipolarons. It was suggested that the high electrical conductivity of sulfuric-acid-treated PPV may be due to formation of a polaron lattice, a regular array of polarons.

Massardier *et al.* (1994) used ^{1}H NMR and UV spectroscopy to follow the kinetics of p-xylylene tetrahy-drothiophenium dichloride salt polymerization in the presence of sodium hydroxide at 3 and 20°C. The consumption of sodium hydroxide was closely related to the production of sulfide. Beside the polymerization reaction, side reactions were detected which were favored by increasing the reactants concentration as well as the temperature.

2.4 Electroviscoelastic Effect in ER Elastomer

While most of researches have been focused on ER fluids, which are normally suspensions of polarizable particles in an insulating oil, however, recent attentions are focused on certain materials based on elastomers which are loaded with polarizable particles or piezoelectric materials as shown in Figure 2.4. It has also been envisaged for some time that electric fields can control the viscoelasticity of elastomers. Polarizable particles can be dispersed in elastomeric materials to create ER elastomers, which may be considered as solid analogs of ER fluids. However, ER elastomers have quite different characteristics. The most noteworthy is that the arrangement of particles is locked within the elastomeric matrix. Therefore, these materials are intended to operate in the elastic regime, while ER fluids typically operate in the post-yield and steady-flow regimes. For appropriate applications, the advantages of ER elastomers over ER fluids are no leakage, no attrition or sedimentation of particles, and possibly higher dielectric strength. In addition, there is the possibility of producing custom-made ER objects of exactly the right shape and size for the application. An ER elastomer also has advantaged for studying the mechanism of the ER effect, as the morphology of the material does not change during measurement and can be determined precisely, atleast in principle.

Information about the ER mechanism provides a basis for selection of materials and morphologies to achieve the desired responses.

Electromechanical response of polydimethylsiloxane (PDMS) dielectric gel was investigated by Bohan and Krause (2001). The samples were cured between two flexible electrodes and the displacement of the electrodes when an electric field was applied was observed by using an optical microscope. The pure PDMS gel showed a small response compared to that of PDMS gels blended with an electrorheological fluids and the composite gel displacement was greatest using 60/40 PDMS/ERF combination.

Krause *et al.* (2001) studied the electromechanical response of polymeric gels. The samplewere prepared by curing of electrorheological fluids, polyaniline (PANI) particles suspended in PDMS fluids, in the matrices of cross-linked PDMS networks (XPDMS). The response of composite gel systems was found to be fast, occurring in ~100ms, depending on the compression modulus than the gel containing random PANI particles by an order of magnitude.

Feher *et al.* (2001) prepared a new type of soft and flexible actuator by blending TiO_2 particles in weakly crosslinked PDMS gels and fabricating the gel into cylinder. The gel was then immersed into silicone oil in order to attain to swelling equilibrium. High DC voltage was applied in a non-contact mode through electrodes and the electric response of the gel was recorded by video camera, they found that the filler-loaded gel cylinder, suspended in silicone oil showed a significant and rapid bending, when an external electric field was applied. The bending behavior was found to be reversible and always occurred towards the cathode.

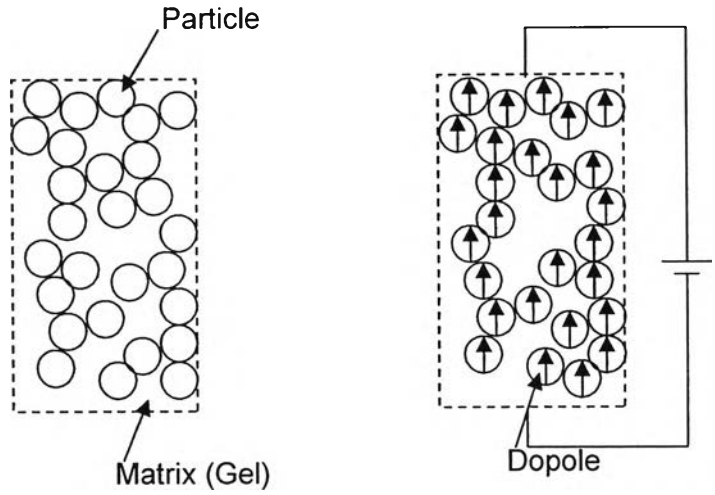


Figure 2.4 Schematic illustration of the electroviscoelastic effect.

2.5 Controlled Drug Delivery Systems

Known widely as controlled release systems, drug-delivering devices have found their way into medical applications during the 1970s with the development of a polypeptide-delivering polymer. Since then, a multitude of devices have been made, from basic systems that incorporate a drug into the matrix of a material, to 'smarter' polymers that deliver drugs when a certain enzyme or pH is encountered. The latter systems have the advantage of reacting to changes in their environment as they arise. Controlled release systems have been developed into such diverse devices as nicotine patches, contraceptive implants, and ocular beads for the treatment of glaucoma (http://www.azom.com.).

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a pre-designed manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events (Peppas, 1997). In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. Other advantages of using controlled-delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, and increased patient compliance.

The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in Figure 2.5a, in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in Figure 2.5b, remaining constant, between the desired maximum and minimum, for an extended period of time depending on the formulation and the application (Gil *et al.*, 1996; Peppas, 1997).

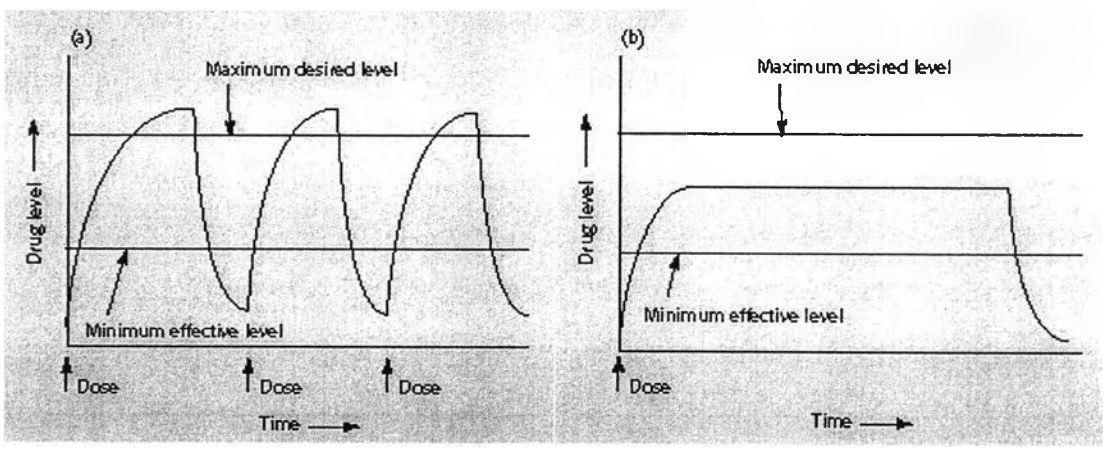


Figure 2.5 Drug levels in the blood with (a) traditional drug dosing and (b) controlled delivery dosing (Peppas, 1997).

2.6 Hydrogel and Therapeutic Agent

Hydrogels are hydrophilic natural three-dimensional networks, held together by chemical or physical bonds. If interstitial space exists within the network, water molecules can become trapped and immobilized, filling the available free volume (Elvira *et al.*, 2002). Hydrogels are among the most promising types of polymers being used for new material development. They have been studied for use in various applications.

Netti *et al.* (1993) reported that the use of fully hydrated hydrogels in the body has been well established. The forces a hydrogel generates on swelling when it is placed in a constrained space were investigated with a view to providing a mechanism for fixing the prosthesis in the intramedullary cavity. A cross-linked poly(2-hydroxyethyl methacrylate) [p(HEMA)] hydrogel was investigated as a potential material. Histological examination showed there was no adverse bone response; bone was growing from the endosteal surface up to and into the hydrogel in the diaphyseal implants and surrounded the hydrogel in the metaphysis.

Beruto *et al.* (2004) demonstrated that a new thermodynamic and kinetic model that describes the relationship between the water self-diffusion coefficient, D, in hydrogel contact lenses. For the contact lenses investigated, the oxygen permeability turned out to be only a quadratic function of equilibrium water content, despite the fact that the fraction of the ''free'' water molecules can be as high as 50%.

Crompton *et al.* (2007) found that thermally responsive chitosan/GP hydrogels provided a suitable 3D scaffolding environment for neural tissue engineering. To improve cell adhesion and neurite outgrowth, poly-D-lysine (PDL) was immobilised onto chitosan via azidoaniline photocoupling. Increase in PDL concentrations did not alter cell survival in 2D cultures but neurite outgrowth was significantly inhibited. Neurones exhibited larger cell bodies and sent out single neurites within the macroporous gel.

Because of the presence of certain functional groups along the polymer chains, hydrogels are often sensitive to the conditions of the surrounding environment. This behavior has led to the extensive use of hydrogels in controlled

drug delivery systems and in membrane separations, where they can respond to changes in the environment and, thus, regulate drug release or solute diffusion (Nho *et al.*, 2005).

2.7 Polyacrylamide Hydrogels

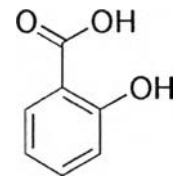
One of the most popular hydrogel polymers is polyacrylamide, PAAM. PAAM and its copolymers have found various applications in controlled drug release due to their high water content. PAAM is hydrophilic and easily swells upon hydration, some grades (based on molecular weight) have shown volume expansion up to 500% at 37 °C (Morita *et al.*, 2000). PAAM is interesting here because of its biocompatibility, non-toxicity, good water permeability and easy manipulation under swelling condition, these characteristics make it ideal for biomedical use especially drug delivery system. The PAAM hydrogels have also gained wide pharmaceutical applications such as drug-delivery matrices or in the form of powders added to a mixture of other incipients for tablet formation.

Prasad *et al.* (2006) studied an in-vito transdrmal permeation of methotrexate loaded into polyacrylamide-based hydrogel patch, across mice skin. Polyacrylamide patches gave the maximum flux as compared to the copolymers of acrylamide and acrylic acid.

2.8 Therapeutic Agent: Salicylic acid model drug

Salicylic acid is a beta hydroxy acid (BHA) with the formula of $C_6H_4(OH)CO_2H$, where the OH group is adjacent to the carboxyl group. This colorless crystalline organic acid is widely used in organic synthesis and it functions as a plant hormone. It is derived from the metabolism of salicin. It is well known as a compound that is chemically similar to but not identical to the active component of aspirin (*acetylsalicylic acid*). In fact, salicylic acid is a metabolite of aspirin, the product of esterase hydrolysis in the liver. Salicylic acid is a key ingredient in many skin-care products for the treatment of acne, psoriasis, calluses, corns, keratosis pilaris, and warts. It works by causing the cells of the epidermis to shed more readily, preventing pores from clogging up, and allowing room for new cell growth. Because

of its effect on skin cells, salicylic acid is used in several shampoos used to treat dandruff. Salicylic acid is also used as an active ingredient in gels which remove warts. Use of concentrated solutions of salicylic acid may cause hyperpigmentation on unpretreated skin for those with darker skin types (Fitzpatrick phototypes IV, V, VI), as well as with the lack of use of a broad spectrum sunblock.



Salicylic acid

Mw 138, Molecular size = 3.28 Å

Figure 2.6 Chemical structure of salicylic acid.

2.9 Controlled Release Mechanisms

Controlled release polymeric systems can be classified according to the mechanism that controls the release of the therapeutic agent as shown in table 2.1.

Table 2.1 Classification of controlled release systems (Heller, 1985)

Type of System	Rate-Control Mechanism
Diffusion Controlled	
Reservoir devices	Diffusion through membrane
Monolithic devices	Diffusion through bulk polymer
Water Penetration Controlled	
Swelling systems	Water penetration into glassy polymer
Chemically Controlled	
Monolithic systems	Either pure polymer erosion (surface erosion) or combination of erosion and diffusion (bulk erosion)
Regulated Systems	
Magnetic or ultrasound	External application of magnetic field or ultrasound to device
Electric field	External application of electric field to device

2.9.1 Diffusion Controlled Systems

Diffusion occurs when a drug or other therapeutic agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale as through pores in the polymer matrix or on a molecular level, by passing between polymer chains. Examples of diffusion-release systems are shown in Figures 2.7.

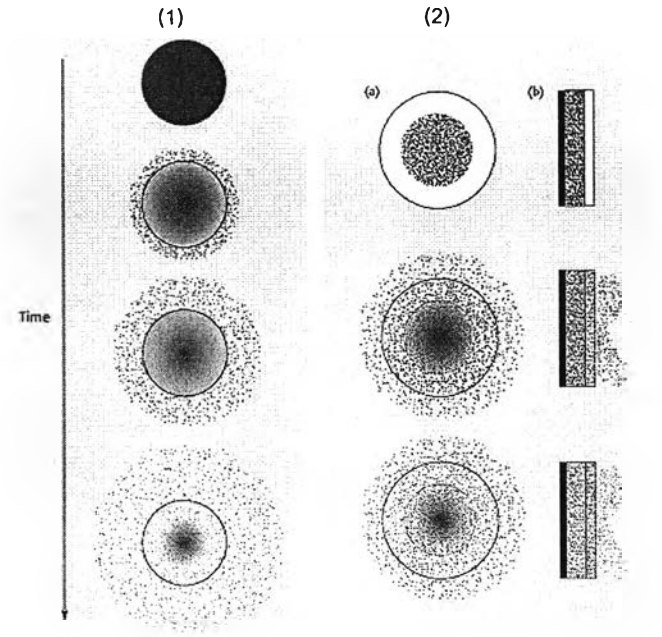


Figure 2.7 Drug delivery from (1) a typical matrix drug delivery system and (2) typical reservoir devices: (a) implantable or oral systems, and (b) transdermal systems (Peppas, 1997).

In Figure 2.7, a polymer and therapeutic agent have been mixed to form a homogeneous system, also referred to as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the therapeutic agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. For the reservoir systems shown in Figures 2.7(2a) and 2.7(2b), the drug delivery rate can remain fairly constant. In this design, a reservoir, whether it is a solid drug, a dilute solution, or a highly concentrated drug solution within a polymer matrix, is surrounded by a film or membrane of a rate-controlling material. The only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. Since this polymer coating is essentially uniform and of a non-changing thickness, the diffusion rate of the active agent can be kept fairly stable throughout the lifetime of the delivery system. The system shown

in Figure 2.7(2a) is representative of an implantable or oral reservoir delivery system, whereas the system shown in Figure 2.7(2b) illustrates a transdermal drug delivery system, in which only one side of the device will actually be delivering the drug. Once the therapeutic agent has been released into the external environment, one might assume that any structural control over drug delivery has been relinquished. However, this is not always the case. For the transdermal drug delivery, the penetration of the drug through the skin constitutes an additional series of diffusional and active transport steps, as shown schematically in Figure 2.8.

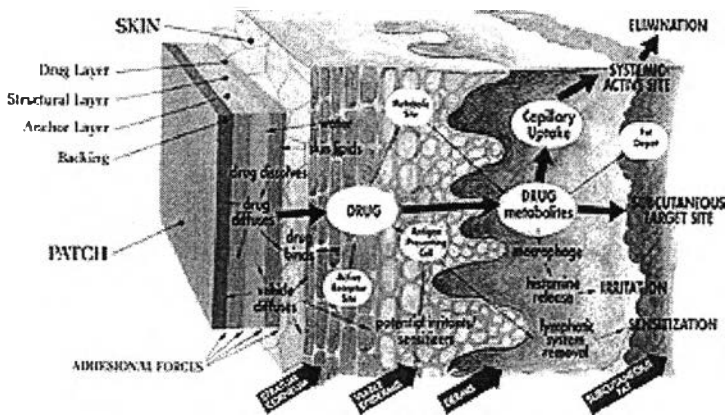


Figure 2.8 Transport processes in transdermal drug delivery (Peppas, 1997).

For the diffusion-controlled systems described thus far, the drug delivery device is fundamentally stable in the biological environment and does not change its size either through swelling or degradation. In these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.

2.9.2 Water Penetration Controlled Systems

It is also possible for a drug delivery system to be designed so that it is incapable of releasing its agent or agents until it is placed in an appropriate biological environment. Swelling-controlled release systems are initially dry, when placed in the body they will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment. Examples of these types of devices are shown in Figures 2.9a and 2.9b for the reservoir and matrix systems, respectively. Most of the materials used in swelling-controlled release systems are based on hydrogels, which are polymers that will swell without dissolving when placed in water or other biological fluids. These hydrogels can absorb a great deal of fluid and, at equilibrium, typically comprise 60–90% fluid and only 10–30% polymer.

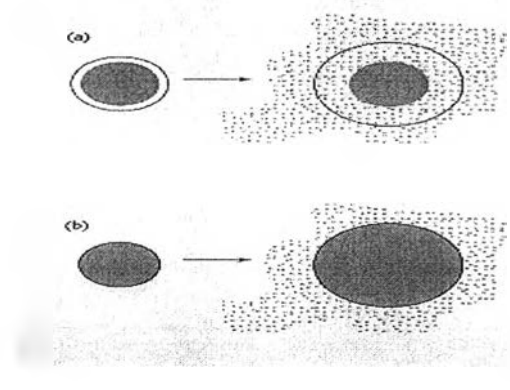


Figure 2.9 Drug delivery from (a) reservoir and (b) matrix swelling-controlled release systems (Peppas, 1997).

2.9.3 Chemically Controlled Systems

All of the previously described systems are based on polymers that do not change their chemical structure beyond what occurs during swelling. These materials degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable, and

progressively smaller, compounds. Degradation may take place through bulk hydrolysis, in which the polymer degrades in a fairly uniform manner throughout the matrix, as shown schematically in Figure 2.10 a. For some degradable polymers, most notably the polyanhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system (see Figure 2.10 b).

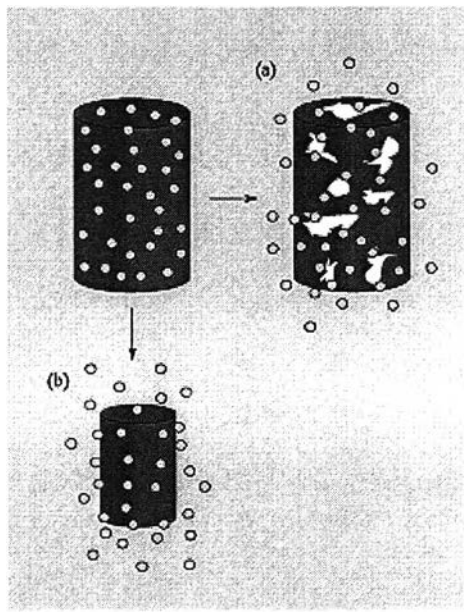


Figure 2.10 Drug delivery from: (a) the bulk-eroding; and (b) the surface-eroding biodegradable systems.

2.9.4 Regulated Systems

The electrically assisted delivery of drugs across the skin, iontophoretic, is the one method that has been successfully employed to overcome some of the obstacles of drug delivery. Iontophoresis is a non-invasive technique which used a mild electric current to facilitate the transdermal delivery of a variety of drug. For enhancing the drug release, the positive charge drug is placed at the positive pole (anode) of patch. Negatively charged drug are formulated within the negative electrode (cathode).

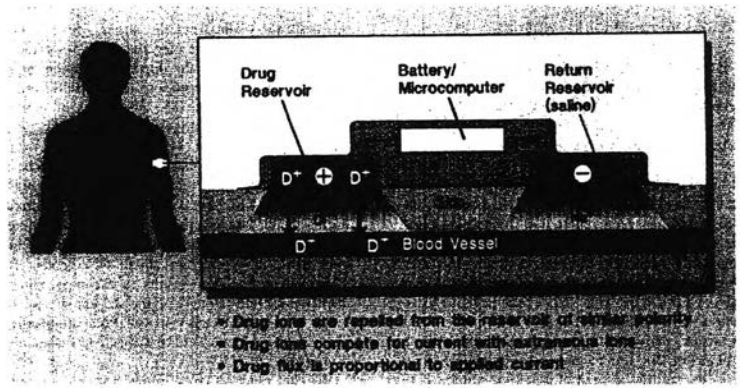


Figure 2.11 Schematic of the components of an iontophoretic patch (Green, 1996).

When the patch is applied to the patient's skin, the drug remains on the outer surface of the skin until the current is allowed to flow. At this time the drug is repelled into and through the skin to elicit a systemic response. This phenomenon is known as electrorepulsion. The mass of drug delivered across the skin is proportional to the applied current and duration of current application (Sage *et al.*, 1992). The electrophoretic diffusion of charged drug within a hydrated membrane results from the combined response to the electrical forces on the drug and its associated counterions in the adjacent electrolyte solution.

The mechanisms for selective controlled transport of drug across hydrogel membranes are (Kost *et al.*, 2001):

1. Electrically and chemically induced swelling of a hydrogel to alter the effective pore size and permeability
2. Electrophoretic augmentation of solution flux within a hydrogel
3. Eletroosmotic augmentation of solution flux within a hydrogel
4. Electrostatic partitioning of charged drug.

Electric field can also cause changes in membrane ionization states affecting membrane hydration and permeability.

Current/voltage conditions for the iontophoretic application should

1. Be sufficiently high to provide a desired delivery rate

2. Not produce any harmful effect on the skin including a permanent alteration in the skin permeability

3. Establish a quatitative relationship between the flux and the applied current/voltage

4. Maintain constancy of the current/voltage during the experimental period.

Okabe *et al.* (1986) reported that the beta-blocker, metoprolol, was introduced transdermally into the veins from a small, square electrode pad (50 cm^2) on the forearm by a newly developed iontophoretic device without causing any detestable skin damage. The appliance generates a sophisticated pulse of 12 V at 50 kHz with 20% duty (4 μs) followed by an 80% depolarizing period (16 μs) which may avoid skin irritation caused by polarization. The drug concentration in plasma increased quickly to the therapeutic level which was maintained for a longer period within one session compared with conventional oral administrations.

Chien *et al.* (1990) demonstrated the feasibility of using iontophoretic delivery devices to facilitate the transdermal transport of hydrophilic charged macromolecules of peptides, such as vasopressin, and proteins, such as insulin, across the skin. In vitro skin permeation studies and in vivo pharmacokinetic and pharmacodynamic studies in diabetic animals suggested that the systemic bioavailability of peptides and proteins, as well as the pharmacodynamic responses, were dependent upon the electronic variables of the iontophoretic delivery device, e.g. waveform, frequency, on/off ratio and intensity of the current applied, physiochemical parameters, e.g. pH and ionic strength, as well as physiological variables, such as treatment of the stratum corneum.

Chen *et al.* (1996) studied a single-compartment iontophoretic permeation cell incorporated with two polyacrylamide hydrogel reservoir devices used to characterize the effect of several electrical parameters on transdermal iontophoretic permeation of LHRH through hairless rat skin. Receptor solutions and skin regions were selected before evaluating the effect of electrical parameters, which included different application patterns, various waveforms and on/off ratios. The difference among various waveforms was not significant. The on/off ratios of pulsed direct current showed a significant effect on transdermal iontophoretic permeation of LHRH, and demonstrated that the higher the on/off ratio (duty cycle),

the greater the skin permeation of LHRH. Duration of current application was more important than amplitude and intensity of current in terms of transdermal iontophoresis. This implies that the skin resistance remained high during current application resulting in lower skin permeation of LHRH for lower on/off ratio.

Ramanathana *et al.* (2001) studied the use of chitosan gels as matrices for electrically modulated drug delivery. Chitosan gels were prepared by acetylation of chitosan and subsequently hydrated to facilitate further studies. 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, results 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.

Bose et al. (2001) studied the electrically assisted transdermal delivery of buprenorphine. Oral delivery of buprenorphine, a synthetic opiate analgesic, was less efficient due to low absorption and large first-pass metabolism. While transdermal delivery of buprenorphine was expected to avoid the first-pass effect and thereby be more bioavailable, the use of electrical enhancement techniques (iontophoresis and/or electroporation) could provide better programmability.

Mutos *et al.* (2007) proposed a novel means of promoting the transfer of uncharged molecules across uncharged polyacrylamide hydrogels. By embedding the polymer skeleton with immobilized silica nanoparticles, they endowed the matrix with a fixed charge, and demonstrated that the application of an electric field enhanced the otherwise diffusion-limited flux of uncharged tracer across the membrane.

The ability of iontophoresis to deliver therapeutic agent to man in an uncomplicated and non-invasive way will conceivably result in improved compliance relative to parenteral administration. One possible feature of the patch is that compliance could be automatically monitored through the memory facility of the internal electronic controller. Adherence to a specific treatment regimen could then

be subsequently displayed, on demand, through various patch LED displays. This type of monitoring may be critical in, for example, the effective treatment of a life threatening illness or in various disease management programs. The electronic controllers are programmable and therefore have the ability to provide complicated dosing features.

Hydrogels and conductive polymers are also called "smart materials" due to their abilities to change their volume or to release substances under external stimuli. Recently, the diffusion and release of a solute from these polymeric systems has emerged as an important issue for the potential application of using the polymeric systems as a controlled drug delivery system (Tao *et al.,* 2005). In fact, both systems, hydrogels and conductive polymers, have been investigated as suitable candidates in controlled drug release applications. Zinger *et al.* (1984) reported the electro-release of glutamate by controlling the ionic flux during the oxidation/reduction of a polypyrrole, PPy, matrix. However, the PPy system has certain limitations: only charged drugs can be released by the electrochemical control; large drugs, even though charged, cannot be easily released through the conducting polymer network; and, the ionic exchange that takes place between the drug and the electrolyte media, independent of the oxidation state of the polymer, diminishes the capacity of an electrochemical control. These findings put constraints on fulfilling two important requisites of the ideal drug release device: the possibility of switching on/off and the precise control of the release rate as functions of the applied potential. In typical drug delivery systems, hydrogels have played a more accepted role than the conducting polymers; but they often have slow responses, which limits the ability to deliver the stimuli efficiently throughout the gel (Lira *et al.*, 2005)

Small *et al.* (1995) prepared and characterized conductive polymer-hydrogel composite. The responsive properties of these materials were investigated. They found that a copunterions open porous structure was maintained during the polymerization. In 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 polymerization at the gel-electrolyte) and outside the gel, would

prevent polymerization 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 hydrophobnicity, calcon, increased.

Li *et al.* (2005) studied the release of heparin from polypyrrole-poly(vinylalcohol) under electric field stimulation. They found that under action of an electric field (1.0 mA), the amount of released heparin was nearly three times higher than that without electric field. Several factors are involved: the electrophoresis of the charged drug, the change in pH due to H^+ migration towards cahode, the expansion of mesh size, and the reduction reaction of the drug doped conductive polymer.

Lira *et al.* (2005) studied the release of safranin dye from a semi-interpenetrating polyaniline -polyacrylamide (PANI-PAAM) network when an electric field was applied. Under electric field (-0.1 V), the amount of released safranin was higher than that without electric field. As PANI chains were reduced, they created a larger free volume in the hydrogel, which facilitated the diffusion of safranin.

2.10 Mathematical Analysis of the Drug Transport Mechanism

In order to study drug transport mechanism from various hydrogels, three diffusion models are generally used to fit the experimental data.

The amount of drug released from a hydrogel at time t (M_t) with respect to the total amount of drug released (M_∞), can be expressed in terms of a power law of time as follows:

$$\frac{M_t}{M_\infty} = kt^n \qquad (2.2)$$

where n is the diffusion scaling exponent. The value of n determines the dependence of the release rate on time that can be related to the drug transport mechanism. The drug transport mechanisms can be identified as Fickian, non-Fickian (anomalous),

linear (zero order), and super case II transport when n is equal to 0.5, $0.5<n<1.0$, 1.0, and $n>1.0$, respectively (Peppass, 1997).

In particular, Higuchi's equation (Peppass, 1997) is associated with the Fickian diffusion of the drug:

$$\frac{M_t}{M_\infty} = k_H t^{0.5}, \qquad (2.3)$$

where M_t/M_∞ is the fractional drug released, k_H is Higuchi's kinetic constant, and t is the release time.

The diffusion coefficients of drug released from the hydrogels are calculated from the slopes of plots of drug accumulation *vs.* square root of time according to Higuchi's equation (A-sasutjarit *et al.*, 2005):

$$Q = 2C_0(Dt/\pi)^{1/2} \qquad (2.4)$$

where Q is the amount of material flowing through a unit cross-section of barrier in unit time, t; C_0 is the initial drug concentration in the hydrogel; and D is the diffusion coefficient of a drug.

Ritger *et al.* (1987) introduced the relation $M_t/M_\infty = kt^n$ which may be used to describe the Fickian and the non-Fickian release behaviors of swelling-controlled release systems which swelled to a moderate equilibrium degree of swelling, and they were prepared by incorporation of a drug in a hydrophilic, initially glassy polymer. Again the diffusional exponent, n, is an important indicator of the mechanism of transport of a drug through the polymer. Analysis was presented for solute release from sheets, cylinders, spheres and polydisperse samples.

2.11 Objective and Scope of Research Work

2.11.1 Electromechanical Responses of a Cross-linked Polydimethylsiloxane

This part investigates the effect of crosslinking ratios and electric field

strength on the electromechanical properties of PDMS; the storage modulus response, the temporal response, the bending response, and its induced electrical force generated between two electrodes.

2.11.2 Dielectrophoresis Force and Deflection of Electroactive Poly(p-phenylene vinylene)/Polydimethylsiloxane Blends

This part investigates the effect of PPV volume fraction and electric field strength on the electromechanical properties of PPV/PDMS blend; the storage modulus response, the temporal response, the bending response, and its induced electrical force generated between two electrodes.

2.11.3 Electric Field Assisted Transdermal Drug Delivery from Salicylic Acid-Loaded Polyacrylamide Hydrogels

1. This part investigates the physiochemical phenomena which are involved inthe electrical controlled release of salicylic acid-loaded polyacrylamide hydrogel systems.

2. This part investigates the effect of crosslinking ratio, and electric field strength on the drug release profile and kinetic of the drug release of salicylic acid-loaded polyacrylamide hydrogel systems.

2.11.4 Electric Field Assisted Transdermal Drug Delivery from Salicylic Acid Doped Poly(p-phynylene vinylene) in Polyacrylamide Hydrogels

1. This part investigates the physiochemical phenomena which are involved in the electrical controlled release of salicylic acid doped poly(p-phynylene vinylene) in polyacrylamide hydrogel system.

2. This part investigates the effect of crosslinking ratio, and electric field strength on the drug release profile and kinetic of the drug release of salicylic acid doped poly(p-phynylene vinylene) in polyacrylamide hydrogel system.