CHAPTER II
LITERATURE REVIEW

2.1 Controlled Drug Delivery Systems

Known widely as controlled release systems, drug-delivering devices 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 2.1a, 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 2.1b, 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).

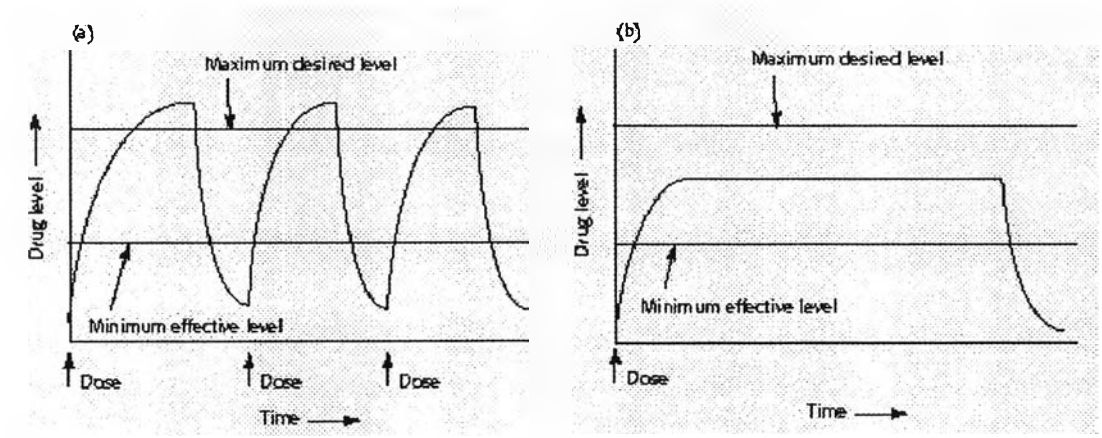


Figure 2.1 Drug levels in the blood with (a) traditional drug dosing and (b) controlled delivery dosing (Peppas, 1997).

2.2 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.

Young *et al.* (1998) investigated and found that PolyHEMA-based hydrogel synthesized by the UV-radiation induced polymerization technique is used to prepare the strength-proved artificial skin in order to improve the handling procedure for curing the burned wound. The strength decreases with increasing amount of the initial water added to the mixture of HEMA (2-hydroxyethyl methacrylate) monomer, ethylene glycol dimethacrylate (EGDMA) crosslinker and benzoin isobutyl ether (BIE) initiator. The artificial skin so fabricated presented several additional characteristics including good wettability, complete transparency, and dimensional changes during water absorption and evaporation.

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).

One of the most popular hydrogel polymers is poly(vinyl alcohol). PVA and its copolymers have found various applications in controlled drug release due to their high water content. PVA 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). PVA 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 PVA 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.

Chicq *et al.* (1986) investigated and found that poly(ethylene-co-vinyl alcohol) was a semicrystalline, hydrophilic copolymer which may be useful in controlled release applications. Transport of water and homologous alcohols at near room temperatures was studied. Theophylline release studies from porous systems of this copolymer showed that both the porosity and the degree of crystallinity were important in the release process, and that the overall release kinetics was dependent on the square root of time. A physical model was presented which described situations of release through water-filled pores and through a continuously swelling polymer.

Pitt *et al.* (1992) studied the controlled release of myoglobin and cytochrome C from spheres coated with a PVA-PGLA (80: 20) blend. The permeability coefficients of naltrexone, naltrexone hydrochloride, cytochrome C, myoglobin and somatotropin in PVA and PVA-PGLA blends (80: 20 and 40: 60) were measured. The permeability was proportional to the water content of the blends, which increased monotonically with the PVA content.

To prolong drug release from the inherently hydrophilic network, PVA may be crosslinked to reduce its macromolecular pore size available for diffusion. The crosslinking process can be carried out either before or after drug loading. A number of methods have been reported for preparation of PVA hydrogels, including chemical methods using a covalent cross-linking agent such as glutaraldehyde and boric acid;

Yeom *et al.* (1996) investigated poly(vinyl alcohol) (PVA) membranes crosslinked with glutaraldehyde (GA) prepared by a solution method for the

pervaporation separation of acetic acid-water mixtures. In the solution method, dry PVA films were crosslinked by an immersion for 2 days at 40°C in reaction solutions which contained different contents of GA, acetone and a catalyst, HCl. Swelling measurements were carried out in both water and acetic acid to investigate the swelling behavior of the membranes. The swelling behaviour of a membrane fabricated at different GA content in a reaction solution was dependent on crosslinking density and chemical functional groups created as a result of the reaction between PVA and GA, such as the acetal group, ether linkage and unreacted pendent aldehydes in PVA.

Li *et al.* (1998) reported that poly(vinyl alcohol) (PVA) hydrogel nanoparticles have been prepared by using a water in-oil emulsion technology plus cyclic freezing–thawing process. The PVA hydrogel nanoparticles prepared by this method were suitable for protein / peptide drug delivery since formation of the hydrogel did not require crosslinking agents. The PVA hydrogel nanoparticles swelled in an aqueous solution and the swelling degree increased with the increase of temperature. The BSA release followed a diffusion-controlled mechanism. The number of freezing–thawing cycle and the release temperature both influenced BSA release rate considerably.

Dai and Barbari (1999) reported that homogeneous poly(vinyl alcohol) (PVA) hydrogel membranes with water contents of 82%, 76% and 72% were prepared by crosslinking PVA with glutaraldehyde. These membranes were then modified to create asymmetry by establishing a glutaraldehyde concentration gradient across the hydrogel thickness. The reaction time and magnitude of the glutaraldehyde concentration gradient were varied to determine the optimum values of permeability and selectivity.

Morita et al. (2000) studied the swelling ability of polyvinyl alcohol (PVA). Some grades of PVA, whose degree of hydrolysis was 96.0 and 97.5 mol%, showed volume expansion of 500% by swelling at 37°C. Based on this unique property of PVA, a new type of controlled release system was developed. The release rate was controlled by the content of PVA and a swelling controlling agent in the core tablet, and the composition and coating level of the film. Emedastine difumarate was

incorporated into the system. Release patterns of zero-order, two phase zero-order, and rapid release after lag-time were obtained with this system.

Taepaiboon *et al.* (2006) found that Mats of PVA nanofibres were successfully prepared by the electrospinning process and were developed as carriers of drugs for a transdermal drug delivery system. Four types of non-steroidal anti-inflammatory drug with varying water solubility property, i.e. sodium salicylate (freely soluble in water), diclofenac sodium (sparingly soluble in water), naproxen (NAP), and indomethacin (IND) (both insoluble in water), were selected as model drugs. The molecular weight of the model drugs played a major role on both the rate and the total amount of drugs released from the as-prepared drug-loaded electrospun PVA mats, with the rate and the total amount of the drugs released decreased with increasing molecular weight of the drugs. Lastly, the drug-loaded electrospun PVA mats exhibited much better release characteristics of the model drugs than drug-loaded as-cast films.

PVA hydrogels have been reported to be useful for the release of both hydrophobic and hydrophilic drugs including salicylic acid, heparin, theophylline, tylosin tartrate, diclofenac sodium,naproxen and indomethacin etc. (Venkatesh *et al.*, 1992; Peppas *et al.*, 1996).

Venkatesh *et al.* (1992) determined that the hydrogel patch formuiations containing 1 %and 21% w/w salicylic acid (PA) are commercially available for the treatment of warts. The release of SA from these formulations was monitored by a procedure reported for in vitro evaluation of transdermal dosage forms. Plots of the fraction of incorporated drug released (up to the release of 60% of the incorporated drug) as a function of square root of time were linear, indicating the matrix diffusion controlled release mechanism. Storage of the packaged formulations under ambient conditions for 9 months caused no change in the rate and extent of SA release. This technique had a potential utility as a quality assurance test for these formulations.

Peppas *et al.* (1996) investigated the influence of possible solute binding on the transport process through the interpenetrating polymeric networks of poly(vinyl alcohol) and poly(acrylic acid) at pH 3 or 6. Diffusion of theophylline, vitamin B12, and myoglobin was analyzed, and diffusion and partition coefficients were

determined. Analysis using the free volume based theory of Peppas and Reinhart indicated that solute binding occurred only in those hydrogels that were in the ionized state. ATR-FTIR spectroscopic studies were used to determine the level of binding in the case of myoglobin in contact with these IPN hydrogels.

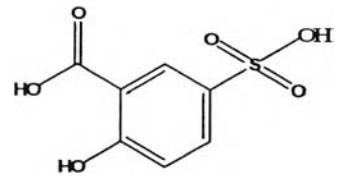
Moretto *et al.* (2004) demonstrated that two antibiotics, tylosin tartrate and oxytetracycline hydrochloride, were entrapped in poly(vinyl alcohol) (PVA) hydrogels (MW 31,000–50,000) by a cryogen procedure obtaining a controlled release system suitable for veterinary application. The results showed that PVA hydrogels was a suitable slow release system for tylosin administration.

Davarana *et al.* (2005) studied the transdermal patch for delivering nicotine for periods of 12–48 h. An inclusion complex formed between the nicotine and cyclodextrine was used in the drug depot. The usefulness of a specially cross-linked polyvinyl alcohol (cross-PVA) membrane was investigated as a rate controlling membrane. These nicotine transdermal patches can be fabricated to obtain a controlled release, zero order systems.

Michael *et al.* (2007) described a drug delivery system based on a physically cross-linked poly (vinyl alcohol) (PVA) hydrogel for the release of Theophylline (TH). A composite was created by freezing an aqueous solution of PVA / NaOH onto a PVA/poly (acrylic acid) substrate forming a strong interface which demonstrated greater physical strength than the hydrogel alone. Such systems have potential for a variety of localised controlled drug delivery applications. TH release rate, depending on the crystalline structure and the dissolution, showed a Fickian release, suggesting that swelling and crystallinity were the controlling mechanisms.

Therapeutic agent: Sulfosalicylic acid model drug

Sulfonic acid derivative are the sulfa drugs which are important as antibiotics such as *Sulfadiazine*, an antibiotic drug that is used in animals.



Sulfosalicylic acid

Mw 254.22, Molecular size = 9.25 A°

Figure 2.2 Chemical structure of sulfosalicylic acid.

2.3 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

2.3.1 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 2.3.

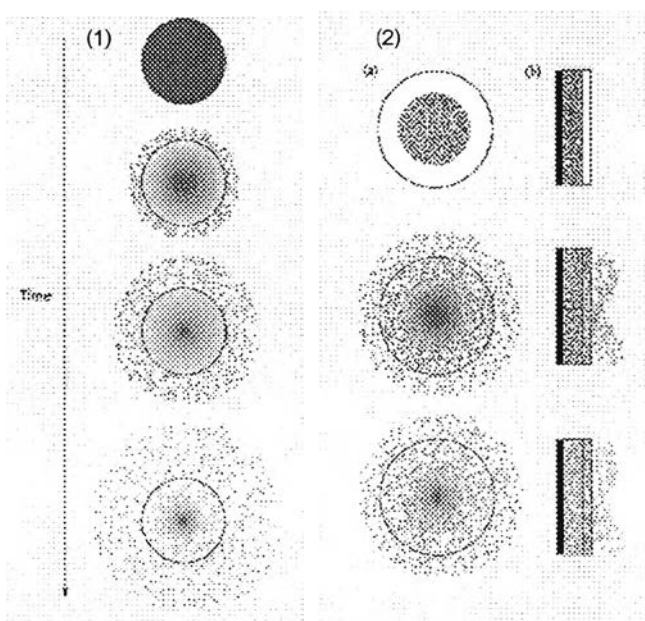


Figure 2.3 Drug delivery from (1) a typical matrix drug delivery system and (2) typical reservoir devices: (a) implantable or oral systems, and (b) transdermal systems (Peppas, 1997).

In Figure 2.3, 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 2.3(2a)

and 2.3(2b), the drug delivery rate can remain fairly constant. In this design, a reservoir whether solid drug, dilute solution, or 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 2.3(2a) is representative of an implantable or oral reservoir delivery system, whereas the system shown in Figure 2.3(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 2.4.

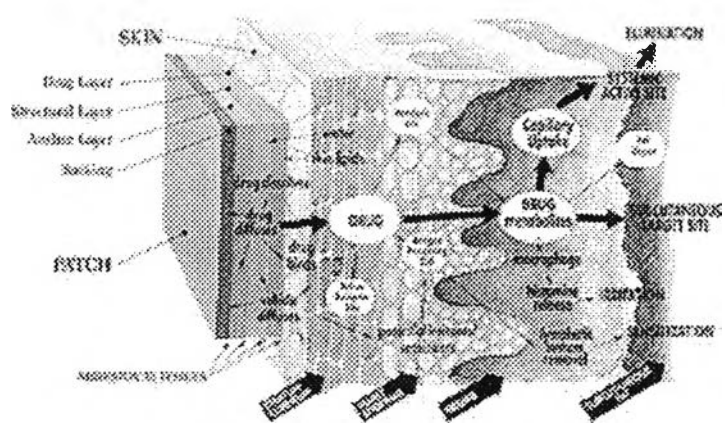


Figure 2.4 Transport processes in transdermal drug delivery (Peppas, 1997).

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.

2.3.2 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 2.5a and 2.5b 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.

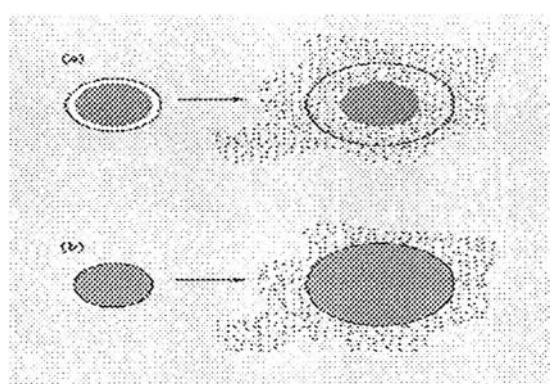


Figure 2.5 Drug delivery from (a) reservoir and (b) matrix swelling-controlled release systems (Peppas, 1997).

2.3.2 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 2.6a. 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 2.6b).

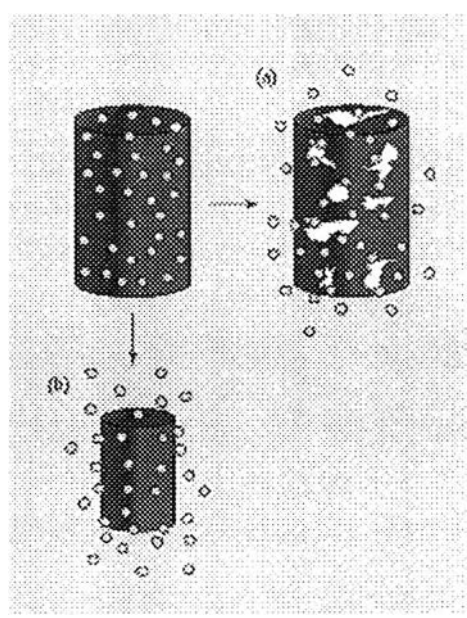


Figure 2.6 Drug delivery from: (a) the bulk-eroding; and (b) the surface-eroding biodegradable systems.

2.3.4 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).

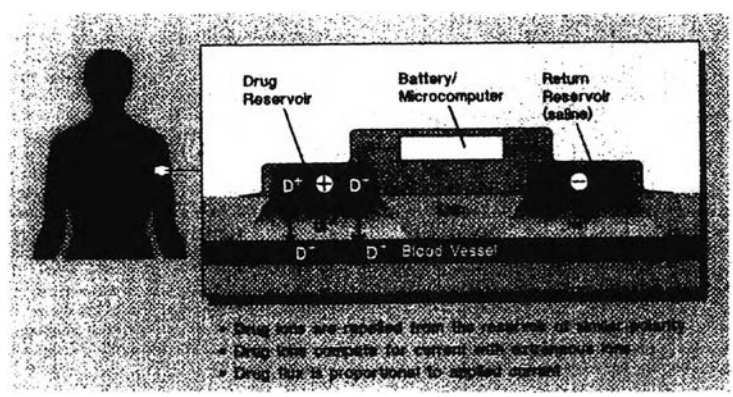


Figure 2.7 Schematic of the components of an iontophoretic patch (Green, 1996).

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).

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.

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.

2.4 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.

Model 1 represents the Fickian model, and is expressed by the following equation (Venkatesh *et al.*, 1992):

$$\frac{M_t}{M_\infty} = k_1 t^n \qquad (1)$$

where M_t/M_∞ is the fractional drug release, k_1 is a kinetic constant and t is the release time and n is the diffusion exponent that can be related to the drug transport mechanism. For a thin hydrogel film, when n = 0.5, the drug release mechanism is the Fickian diffusion.

This mechanism is based on the Higuchi's equation (Serra *et al.*, 2006) which describs the Fickian diffusion of the drug:

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \qquad (2)$$

where M_t/M_∞ is the fractional drug release, k_H is a kinetic constant and t is the release time.

When n = 1, Case II transport occurs, leading to zero-order release. When the value of n is between 0.5 and 1, the anomalous transport is observed.

Model 2 represents a zero-order model and is expressed by the following equation (Serra *et al.*, 2006):

$$\frac{M_t}{M_\infty} = k_H t \qquad (3)$$

Model 3 represents a First-order model and is expressed by the following equation (Liu *et al.*, 2003):

$$M_t = M_\infty\left(1 - \exp(-t/\tau)\right) \qquad (4)$$

where M_t and M_∞ are the amounts of drug release at time t and infinity, respectively, and t is the release time.

The diffusion coefficients of sulfosalicylic acid from the PVA 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):

$$Q = 2C_0(Dt/\pi)^{1/2} \qquad (3)$$

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.