CHAPTER II

LITERATURE REVIEW

2.1 Implantable Controlled-Release Drug Delivery Systems (Chien et al., 1982)

Subcutaneously implantable drug pellets was the first long-term, continuous drug administration, which was developed in 1861 and rediscovered in 1936. Originally subcutaneous implant was composed of drug crystals compressed with or without a small fraction of pharmaceutical excipients into tiny, cylindrical pellet, which could be readily implanted into a subcutaneous tissue by a small skin incision. Subcutaneous tissue is basically a sheet of areolar tissue lying directly underneath dermal tissue. It is rich in fat but poor in nerve network and hemoperfusion. Therefore, subcutaneous tissue is an ideal location for implantation and prolonged drug administration because of ready access, slow drug absorption and low reactivity to the insertion of foreign materials.

It was later found that subcutaneous drug administration via pellet implants had several undesirable drawbacks. The primary difficulty was that the release profile of drug from pellet was not constant and could not be controlled readily, in terms of the precision of release rate and the duration of action. Thus, the clinical use of implantable pellets in human medicine has declined. There are currently only a few steroid pellets commercially available for medication. However, therapeutic benefits of subcutaneously controlled drug administration can be illustrated by comparing with other routes of drug administration. In transdermal drug administration, percutaneous absorption of most drugs is limited by highly impermeable stratum corneum. In oral drug administration, bioavailability of drugs is often subjected to variations in gastrointestinal absorption and biotransformation by hepatic first-pass metabolism. In intravenous drug administration, duration of drug action is short for the majority of therapeutic active agents and frequent injections are necessary. With subcutaneous implants, however, one can gain easy access to systemic circulation to complete drug absorption without aforementioned limitations of transdermal and oral route administration. In addition, subcutaneously implantable drug delivery system presents one unique advantage over parenterally controlled-release system. It permits a readily reversible termination of administration whenever medical and/or personal reasons dictate such a need. These advantages have triggered the research and development of novel, controllable, biocompatible drug delivery systems to replace the pellets for long-term, continuous-release subcutaneous drug administration.

2.1.1 Approaches to Subcutaneous Controlled-Release Drug Delivery Systems

Several approaches other than the conventional drug pellets can be utilized to achieve controlled-release of biologically active agents via subcutaneous implantation. The following approaches have been successfully explored and applied:

2.1.1.1 Membrane Permeation-Controlled Drug Release

This type of controlled-release drug delivery system is fabricated by encapsulating a reservoir of drug crystals inside a capsule made from bio-compatible polymers with a well-defined wall thickness. The controlled-release of the encapsulated drug crystals is achieved by dissolution of drug crystals in the polymer, diffusion of drug solute molecules across the whole thickness of the capsule wall, and then release of drug molecules into the surrounding tissue fluid at the site of implantation. The rate of drug release (Q/t) from this system is determined by the solubility (C_p) and diffusivity (D_p) of drug in the polymer membrane with thickness of δ_p as mathematically described by the simplified relationship:

$$\frac{Q}{t} = \frac{C_p D_p}{\delta_p} \qquad 2.1$$

This subcutaneously implantable drug delivery system is theoretically expected to give a constant (zero-order) release.

2.1.1.2 Matrix Diffusion-Controlled Drug Release

Fabrication of this type of controlled-release drug delivery system is homogeneously dispersing a dose of micronized drug particles throughout a polymer matrix, which is molded into rod-, disc-, bead-, or pellet-shaped implants. Controlled-release of the embedded drug particles is achieved by dissolution of drug particles in the surrounding polymer matrix, diffusion of drug solute molecules across drug depletion zone, which is growing in thickness, and then release of drug molecules into the surrounding tissue fluid at the site of implantation. The instantaneous rate of drug release (dQ/dt) from matrix diffusion-controlled drug release system is determined by the square root of drug loading ($A^{1/2}$), the square root of drug solubility in the polymer ($C_p^{1/2}$) and the square root of drug diffusivity in the polymer matrix ($D_p^{1/2}$) as mathematically described by the relationship:

$$\frac{dQ}{dt} = \left(\frac{AC_p D_p}{2t}\right)^{\frac{1}{2}} \qquad 2.2$$

The drug release flux obtained from integration of equation (2.2) is defined by

$$\frac{Q}{t^{\frac{1}{2}}} = [(2A - C_p)C_p D_p]^{\frac{1}{2}} \qquad 2.3$$

Equation (2.2) suggested that the rate of drug release from this type of drug delivery system is time-dependent and is decreased with the square root of time. It is the result of a progressive increase in thickness of drug depletion zone as a function of time.

2.1.1.3 Matrix Erosion-Controlled Drug Release

Matrix erosion-controlled drug delivery system is produced by homogeneously dispersing a dose of micronized drug particles throughout a polymer matrix made from bioerodible or biodegradable polymer, which is then molded into pellet- or bead-shaped implants. The controlled release of the embedded drug particles is possibly made by the combination of polymer erosion and matrix diffusion. The instantaneous rate of drug release (dQ/dt) from this type of drug delivery system is determined by the effective surface area of polymer matrix (S_m), the diffusion coefficient of drug in water or release medium (D_w), the porosity of polymer matrix (ε), the solubility of drug in water or release medium (C_w), the initial drug concentration (C_0), and the tortuosity of pore structure (τ) as mathematically described by the following relationship (Wandee Im-Emsap, 2002):

$$\frac{dQ}{dt} = \frac{S_m}{2}\left[\frac{D_w \varepsilon * C_w(2C_0 - \varepsilon C_w)}{\tau * t}\right]^{\frac{1}{2}} \qquad 2.4$$

The rate of drug released from matrix erosion-controlled drug release system is not constant. It depends on a combination of matrix diffusion (square root time kinetics) and matrix erosion (first-order kinetics).

2.1.1.4 Osmotic Pressure-Driving Drug Release

This type of controlled-release drug delivery system is created by encapsulating a concentrated drug solution inside a collapsible compartment with one delivery orifice, flexible, and impermeable walls, which is coated with a sealed layer of osmotic active salt contained within a semi-permeable membrane on its external surface. When the device is subcutaneously implanted, the semi-permeable membrane controls the rate at which the osmotic active agent imbibes extra-cellular fluid. Thus, an osmotic pressure is generated to exert on the collapsible compartment and serves as the driving force to pump the contents of the drug reservoir through the delivery orifice. The pumping rate of a drug formulation is directly proportional to the water permeability (P_w), the effective surface area of the semi-permeable membrane (S_m) and the net osmotic pressure gradient (π_s-π_e) between the saturated solution of osmotic active salt in the system and the environment, where the system is implanted. The rate of drug release can be defined by a simple relationship:

$$\frac{Q}{t} = P_w S_m (\pi_s - \pi_e) \qquad 2.5$$

Equation (2.5) suggests that the osmotic pressure-driving drug delivery system gives a constant rate of drug administration.

2.1.1.5 Vapor Pressure-Driving Drug Release

This drug delivery device consists of a hollow titanium disc divided into two chambers by a freely movable titanium bellows. The inner chamber is loaded with an infusate. The outer chamber contains a fluorocarbon liquid that vaporizes at body temperature and exerts a vapor pressure above atmospheric pressure. The vapor pressure propels the infusate through a series of filters, a flow-regulating resistance element, and a silicone delivery cannula into a vein at a constant flow rate. The rate of drug release (Q/t) through the regulator is governed by the poiseuille relationship:

$$\frac{Q}{t} = \frac{\pi d^4 \Delta P}{128 \mu l} \qquad 2.6$$

where π is a constant (3.1416), d is the inner diameter of delivery cannula, ΔP is the pressure difference between the vapor pressure in the pump and the atmospheric pressure, μ is the viscosity of the infusate solution, and l is the length of the delivery cannula. Equation (2.6) suggests that the flow rate of infusate solution can be adjusted readily by varying the length and diameter of the delivery catheter and/or altering the viscosity of the infusate solution.

2.1.2 Development of Implantable Controlled-Release Devices

A number of subcutaneously implantable controlled-release drug delivery systems have recently been developed and are illustrated as following.

2.1.2.1 Silicone Capsule Implants

This type of subcutaneous implant has been developed for long-term continuous administration of contraceptive hormone. Steroid drug is encapsulated inside a silicone capsule in which drug release controlled by membrane permeation. The release rate is constant as attributed on the basis of equation (2.1). Mesogestrol acetate-releasing silicone capsule is an example of successful formulation. From animal experiment, the actual accumulations of mesogestrol acetate in kidneys of rabbit and hamster were approximately 50 times less than that found in these animals given the same steroid by oral administration. Anti-inflammatory drugs and antineoplastic agents are other two drug groups have been formulated in silicone capsule type. The administration of non-steroidal anti-inflammatory drugs at a controlled rate via subcutaneous implantation of silicone capsules has improved the anti-arthritic efficacy by approximately three times over the conventional drug administration via daily subcutaneous injections. For antineoplastic drug-releasing silicone capsules, the administration via interstitial implantation directly into the

center of the tumor mass has significantly improved the antineoplastic efficacy of the drugs while the mortality rate has been minimized.

However, the therapeutic efficacy of this kind of implant declines as duration of subcutaneous residence increases. This incident may be related to the reduction of subcutaneous bioavailability of drug due to the formation of a continuous wall of fibrotic tissue of variable thickness around silicone capsule.

2.1.2.2 Polymeric Pellet Implants

A modified polymeric pellet type has primordially been developed to overcome the slow-release characteristics of poor aqueous solubility of drug such as morphine-cellulose pellet. This implant is produced by homogeneously dispersing morphine crystals throughout the polymer matrix and then tableting in a mold. As expected from equation (2.2), drug release under a sink condition is not constant but follows the square root time kinetics. After implantation, the pellet tends to be encapsulated by membraneous tissues and the bioavailability of drug diminishes. Moreover, the pellet also quickly becomes soft and mushy. The retrieval of the pellet from the site of implantation is extremely difficult. To overcome these drawbacks, novel polymers have been extensively investigated to be a suitable material.

2.1.2.3 Biodegradable Pellet Implants

This type of implant has been developed to overcome the drawback of polymeric pellet implant, which does not release the drug at zero-order release kinetics. This is due to the fact that the thickness of drug depletion zone is getting thicker and thicker as release of drug proceeds continuously. If the area of the drug delivery device maintains a constant value during the release period; that is the thickness of drug depletion zone unchanged because of degradation of polymer matrix, the zero-order kinetics can also be achieved. Therefore, drug release profile from biodegradable pellet implant is controlled by the combination of biodegradation of the polymer and drug diffusion. When the rate of drug release by diffusion is greater than the rate of biodegradation of the polymer, drug release follows square root time kinetics as observed in naltrexone-releasing cholesterol/glyceride pellet. Moreover, the study of biodegradation of co-(lactide/glycolide) polymers during subcutaneous implantation revealed that molecular weight of the polymers in the removed implants was reduced following first-order kinetics. This finding indicates the difficulty of achieving a constant rate of drug released from this type of subcutaneous implant. However, the biodegradability in the body is an advantage of this kind of implant, so that the surgical removal of implant at the end of administration is not a problem. Several investigations have been carried out to develop this group of implants.

2.1.2.4 Osmotic Minipump Implants

A typical osmotic pressure-powered drug delivery system commercially available for subcutaneous implantation and continuous drug administration at a controlled rate is the Alzet osmotic minipump system as shown in

Figure 2.1. One of the currently available models is cylindrical in shape, with 0.6 cm in outside diameter and 2.5 cm in length, and has an overall device volume of 0.6 ml. The collapsible drug reservoir compartment has a volume of 0.17 ml and is made from a thermoplastic hydrocarbon elastomer. The wall thickness of the drug reservoir compartment is very thin, 0.3 mm, to ensure the complete collapse of the reservoir. The external wall of the drug reservoir compartment is coated with a sealed layer of osmotic active agent, e.g., KCl or NaCl, by dipping it into a suspension of salt and subsequently drying at 50°C. The semi-permeable membrane is then coated by dipping the osmotic driving agent-coated reservoir into a homogeneous solution of an appropriate cellulose ester in organic solvent and subsequently drying at 50°C.

Alzet osmotic minipump system can be used for subcutaneously or intra-peritoneally controlled administration of a number of therapeutically active agents such as insulin, morphine sulfate, endorphin, propranolol, haloperidol, prostaglandin E_2, luteinizing hormone releasing factor and agonists, estradiol, gonadotropin releasing hormone, antigens, ascitic fluid antibody, deoxycorticosterone acetate, dopamine and dopamine antagonists, gentamicin sulfate, and vasopressin.

2.1.2.5 Implantable Infusion Pump

An implantable infusion pump has been developed on the basis of the physical concept that a vapor in equilibrium with its liquid phase exerts a constant vapor pressure at a given temperature regardless of volume. A typical model consists of a hollow titanium disk, divided into two chambers by a freely movable titanium bellows. The inner chamber contains the infusate solution, and the outer chamber contains a fluorocarbon fluid as displayed in Figure 2.2. At body temperature (37°C), the vapor pressure produced by the vaporization of this fluorocarbon fluid is approximately 300 mmHg greater than the atmospheric pressure and provides the power needed to work the bellows and propel the infusate through a series of bacterial filters, a flow-regulating resistance element, a silicone polymer delivery cannula and finally into a vein. This device has been used for long-term intravenous heparin infusion for refractory thromboembolic disease and the controlled infusion of insulin for treatment of diabetes.

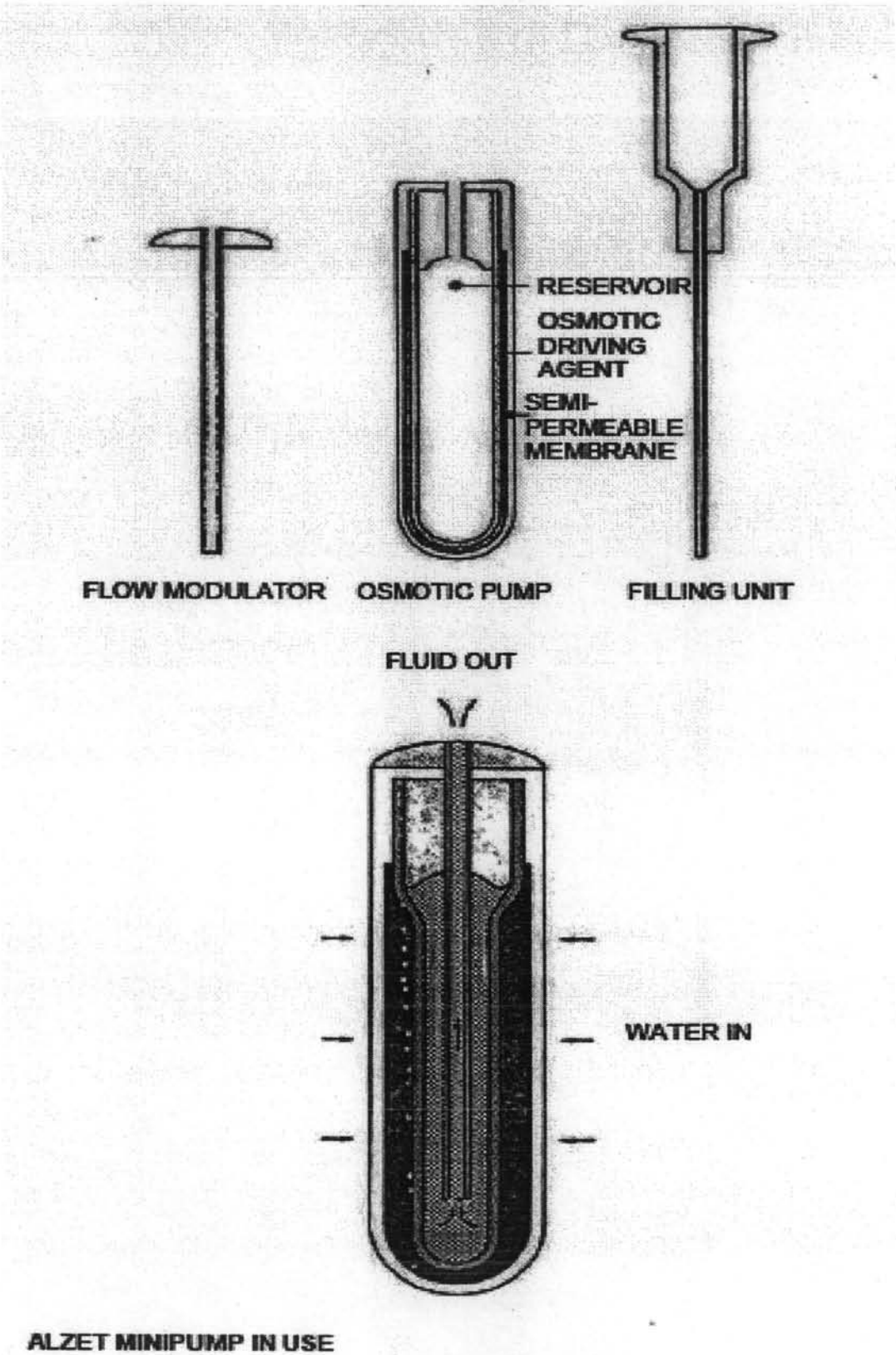

Figure 2.1 Schematic illustration of the Alzet osmotic minipump system (Alza Corporation, Palo Alto, California) (From Chien et al., 1982)

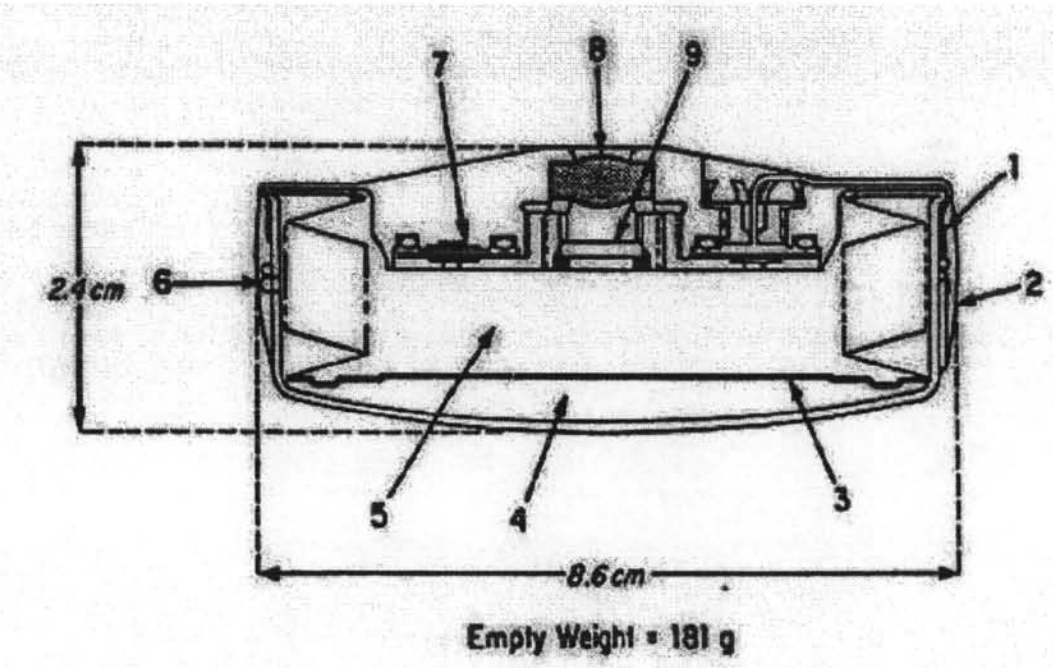

Figure 2.2 Schematic illustration of the implantable infusion pump (Infusade, Metal Bellows Corporation, Sharon, Massachusetts): (1) flow regulator; (2) silicone polymer coating; (3) bellows; (4) fluorocarbon (outer) chamber; (5) infusate (inner) chamber; (6) fluorocarbon fluid filling tube (permanently sealed); (7) filter assembly; (8) inlet septum for percutaneous refill of infusate; (9) needle stop (From Chien et al., 1982)

2.1.2.6 In Situ Forming Implants (Wandee Im-Emsap, 2002)

This kind of implant consists of drug dissolved or dispersed in a biodegradable polymer solution, which is subcutaneously injected and forms a single unit implant in the body. The preferred thermosetting polymers used for the systems are low degree of crystallization and hydrophobic in order to enhance their solubility in the solvents such as polylactides, polycaprolactones, and copolymers of these with glycolide (Dunn et al., 1998). The preferred biocompatible solvents used for the systems are N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide and acetone because of their solvating ability (Dunn, English et al., 1994a, Dunn, English et al., 1994b). Although the system consists of only one phase containing drug in polymer solution, each component is separately stored before the time of administration in order to prevent incompatibility or instability. Upon injection, the biocompatible water-soluble solvent diffuses out of the polymer while water from body fluid permeates into the polymer matrix. Due to insolubility of polymer in water, it precipitates upon contact with water. Thus, the solidified implant is formed. This system has been initially described for doxycycline hyclate (Dunn, Tipton et al., 1994) by researchers at Atrix Laboratories.

In the case of polymer solution containing temperature sensitive polymers, these polymers are hydrated below critical solution temperatutre and dehydrated above. This leads to network shrinking above the critical temperature, which diminishes the network volume and thereby releases incorporated substances. This type of polymers is exemplified by poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO) block copolymers under the trade name of Pluronics® or Poloxamer® having the sol-gel phase conversion at the body temperature. They have been approved by FDA for applications in food additives, pharmaceutical ingredients and agriculture products (Qui and Park, 2001).

The pH sensitive polymers have also been used in development of this type of implant. These polymers usually contain acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that either accept or donate protons in response to environmental pH changes (Qui and Park, 2001). The reversible ionization at an inherent pH range dramatically affects their polarity. The change of polarity alters swelling of the polymer network, which controls permeation of a water soluble solute through the gel network. Chitosan is an example of this polymer group. It dissolves in aqueous solution via the protonation of its amine groups in acidic environment at pH below 6.2. At pH exceeding 6.2 it is neutralized in aqueous solution. This leads to the formation of a hydrated gel-like precipitate.

The in-situ forming system normally exhibits initial drug burst release due to a lag time between the injection and the formation of the solid implant. The subcutaneous and intramuscular environment have limited amount of water and fluid flow in human adipose tissue, which may range from 7 to 53 ml/100 g per min (Shively et al., 1995). Thus, the formation of implant is not rapidly adequate. The drug is likely diffused out along the water soluble solvent flux into the surrounding tissues resulting in a high initial release that causes local or systemic toxicity. In attempts to reduce the initial burst release, it is necessary to have polymer

concentration used in the system in the range of 40-55 % w/w. It was evidenced that increase of the polymer content led to decrease drug burst release (Lambert and Peck, 1993). However, high polymer concentration also increases the solution viscosity. The in-situ forming system is often encountered with injectable problem when administered via standard size of syringe and needle. Otherwise large needles such as 18-20G are used, thus, causing pain to patients. Furthermore, the muscle tissues come into immediate contact with solvent in the system after injection. This increases a potential of acute myotoxicity and skeletal muscle damage (Kranz et al., 2001).

2.2 Development of Matrix System with Constant Release Rate

One major drawback of matrix diffusion-controlled release system is inability to achieve the zero-order release kinetics. This is due to the fact that the thickness of drug depletion zone, through which the drug molecules have to pass before they are released, is getting thicker and thicker as release of drug continuously proceeds. Therefore, the rate of drug release decreases with the reciprocal of the square root of time. Rippe and Johnson (1969), Cobby et al. (1974), and Hsieh et al. (1983) have declared that the shape of a matrix is a factor affecting drug release, so that several attempts have been done in development of new designs of matrix system in order to achieve the zero-order or near zero-order release kinetics for longer than two decades.

2.2.1 Hemipheric Polymer-Drug Matrix Design

Hsieh et al. (1983) fabricated this system design in controlling release of small molecules and macromolecules in order to achieve the zero-order release kinetics. The design displayed a hemispheric polymer-drug matrix coated with an impermeable material, except for a small cavity cut into the center of the flat surface.

Due to theoretical analysis describing drug released from matrix device based on Fick's law diffusion, the instantaneous release rate is represented in the following equation;

$$\frac{dQ}{dt} = -DS_m \frac{dc}{dr} \qquad 2.7$$

where Q is the mass of drug released, t is the time, D is the drug diffusion coefficient, S_m is the effective surface area for drug release, c is the drug concentration and r is the distance from the diffusion source to the release surface. It can be seen from equation (2.7) that the release rate decreases as the distance r increases; that is, the release rate is inversely proportional to the distance which the drug must travel from within the matrix to the matrix surface. The inwardly-releasing hemisphere, which drug release only occurs through a cavity in the center, has been fabricated in order to increase the available area, where drug can be released, so as to compensate for the increase in diffusion distance of drug transport. Theoretical analysis of release equation for this device has been derived under these assumptions;

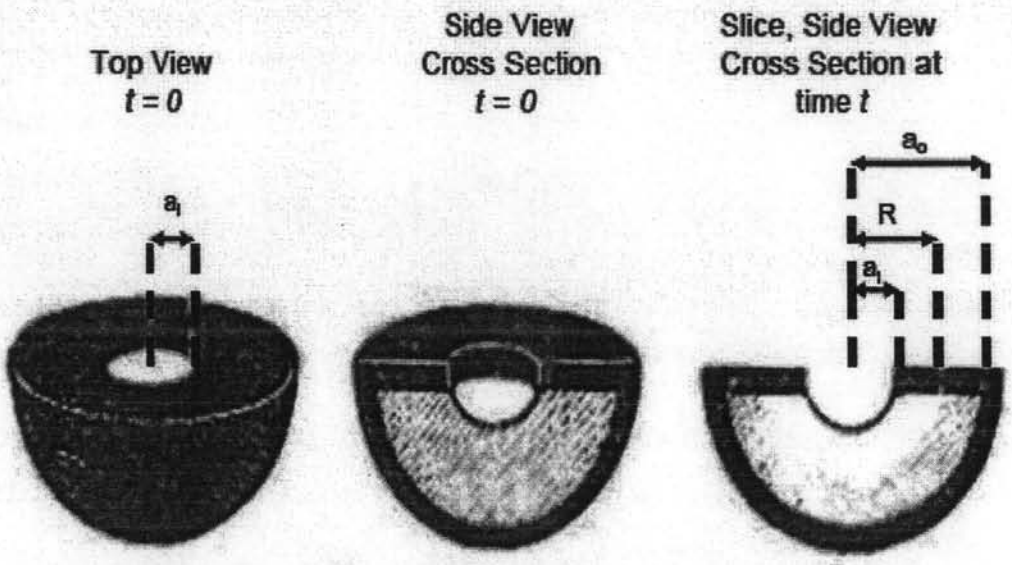

Figure 2.3 Diagram of an inwardly-releasing hemisphere: a_i is the inner radius; a_o is the outer radius; R is the distance to the interface between the dissolved region (white area) and the dispersed zone (diagonal lines); and black represents coated regions through which release cannot occur (From Hsieh et al., 1983)

(i) The amount of drug present per unit volume (C_0) is substantially greater than drug solubility per unit volume of the release media (C_s).

(ii) The solid drug firstly dissolves from the surface layer, where is depleted of drug, the next layer begins to be depleted, so that the interface between the region containing dissolved drug and dispersed drug moves into the interior as a front.

(iii) The release process occurs under infinite sink conditions.

Then, the release rate for the hemisphere device can be written as the following equation (Hsieh et al., 1983);

$$\frac{dQ}{dt} = 2\pi C_s D a_i \left(\frac{R}{R - a_i}\right) \qquad 2.8$$

where Q is the mass of drug released, t is time, π is constant value, C_s is drug solubility in the release media, D is diffusion coefficient of drug in matrix, a_i is radius of the cavity, and R is radial distance to interface between dissolved and dispersed drug within the matrix.

From equation (2.8), $R-a_i$ becomes equal to R when $R \gg a_i$. Equation (2.8), then, can be reduced to the following equation;

$$\frac{dQ}{dt} = 2\pi D C_s a_i \qquad 2.9$$

Each of the terms in equation (2.9) is a constant. Thus, release rate of a hemispheric device with small a_i is essentially constant. The theoretical analysis was agreed with the experimental data obtained from Hsieh et al. (1983). Their study addressed that hemispheric matrices acted as constant release systems for both sodium salicylate and bovine serum albumin, which are represented as small molecule and macromolecule, respectively.

2.2.2 Cylindrical Polymer-Drug Matrix with a Central Hole

In the pharmaceutical field a cylindrical shape is often chosen in the preparation of solid dosage forms. This shape involves a decrease in the releasing area of the drug core as the diffusion path length increases. A cylindrical polymer-drug matrix with a hole bored in the center of the flat surface through both sides of the matrix laminated all surfaces with an impermeable coating except a central hole was fabricated by Vandelli and Cameroni (1993a; 1993b). This type of polymer-drug matrix allows the polymer swelling following pseudo-zero order kinetics regardless of the drug loaded. When matrix swelling occurs before drug release, the drug release is controlled by swelling process. This supported the finding that the release of theophylline, a sparingly water-soluble drug, from this kind of device was controlled by swelling process and exhibited a constant release according to the effect of matrix geometry (Vandelli and Cameroni, 1993b).

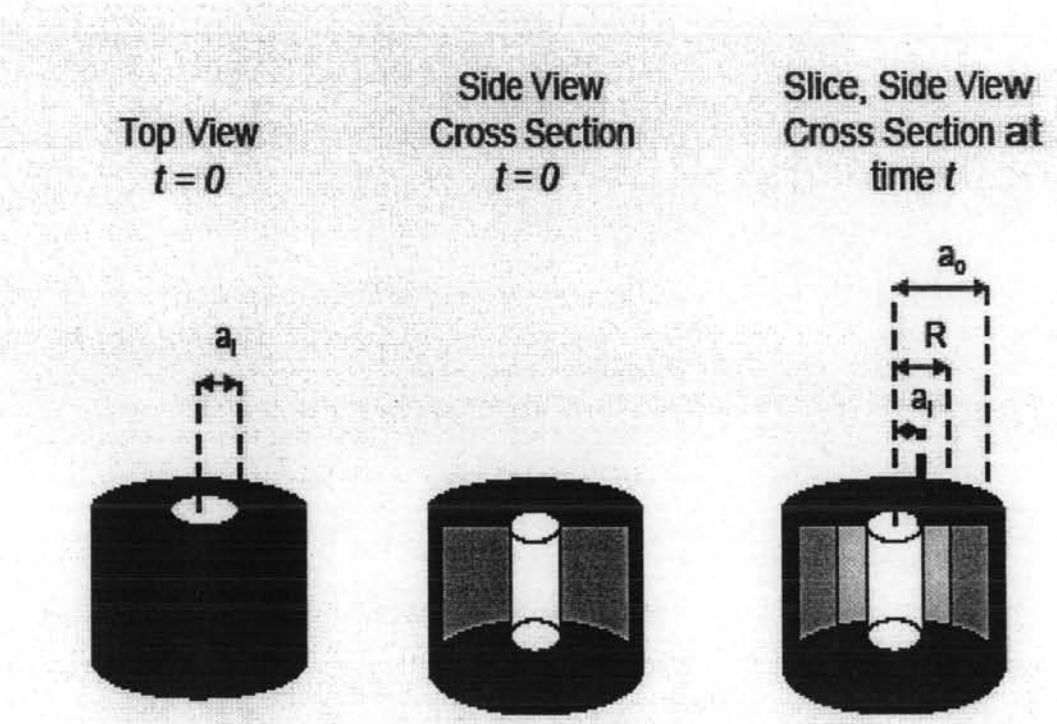

Figure 2.4 Diagram of a perforated matrix in a cylindrical shape: a_i is the inner radius; a_o is the outer radius; R is the distance to the interface between the dissolved region (light gray area) and the dispersed zone (dark gray area); and black representing coated regions through which release cannot occur

However, the major problem encounters in the fabrication procedures of the former two devices is a technique for puncture a hole uniformly. This is very critical to achieve reproducibility. The improved techniques to create holes in the center of matrix devices should be explored.

2.2.3 Geomatrix® Technology (Conte et al., 1993; Conte and Maggi, 1996; Conte and Maggi, 2000; Abdul and Poddar, 2004)

Geomatrix® technology was initially designed to achieve a zero-order release rate by combining a time-dependent control of the hydration rate of the system with the reduction of the tablet surface exposed to the dissolution medium. In fact, the Geomatrix® system is a multi-layer tablet, which comprises of a matrix core containing the active solute and one or more barriers applied to the core directly during the tableting process. The barriers delay the interaction of active solute with dissolution medium by limiting the surface available for the solute release and controlling solvent penetration rate at the same time. In this device, the barrier layers prevent the water penetration through the protected core for some duration. This results in reduction of hydration rate and controlling area for solute release at the core. Thus, burst effect can be smoothened and the release can be maintained at a relatively constant level during swelling and erosion process of the barrier layers. After this phase, during the subsequent portion of the dissolution process, the erosion of these swollen barriers is dominated and the available surface for drug release slowly increases. In this way the decrease of delivery rate due to the increase of diffusion path-length is counterbalanced by the simultaneous increase of the available area for drug release.

A long time was devoted to the optimization of suitable barrier formulations that could be applied on the core directly during the tableting process. The development of the barrier formulation was carried out through two different approaches. The first was based on the use of inert insoluble polymer, ethyl cellulose, and the second was based on the use of hydrophilic swellable polymer, hydroxypropylmethylcellulose. In case of an inert impermeable polymer applied on the tablet faces, these barriers tend to crack and detach themselves from the core within hours after water immersion. This effect is due to core volume expansion upon water immersion by polymer swelling. This stresses the outer barrier layer, which does not expand to accommodate the swelling of the core. In any way, the swellable barriers show a more homogeneous system in which both the barrier and the core may simultaneously swell without any internal stress during the dissolution process.

Maggi et. al. (2000) declared that release profiles of the three-layer matrices with the same cores and different barriers were different. The barriers containing polymers of higher viscosity were stronger reduction in drug release rate than those containing polymers of lower viscosity. In the same way, the cores containing the polymers of higher viscosity released drug at a lower rate than those containing the polymers of lower viscosity. However, the dissolution profiles of the Geomatrix® three-layer systems with the same barriers but with cores containing different polymers were similar. This indicated that the core composition had less influence on

the drug delivery modulation, while the barriers played the leading role in controlling drug release from this kind of device.

The Geomatrix® system is a unique drug delivery device, which overcomes the major disadvantage of non-linear release associated with most diffusion controlled matrix devices. The rate of drug released from Geomatrix® device can be easily modulated by varying the formulations of the layers. This system also has the advantage of being compatible with conventional manufacturing methods.

The first product based on the Geomatrix® technology was launched in 1992 in the United States of America. It is Dilacor XR of Rhone Poulenc-Rorer, a device for the 24-hours extended release of diltiazem hydrochloride, which is a drug of high solubility.

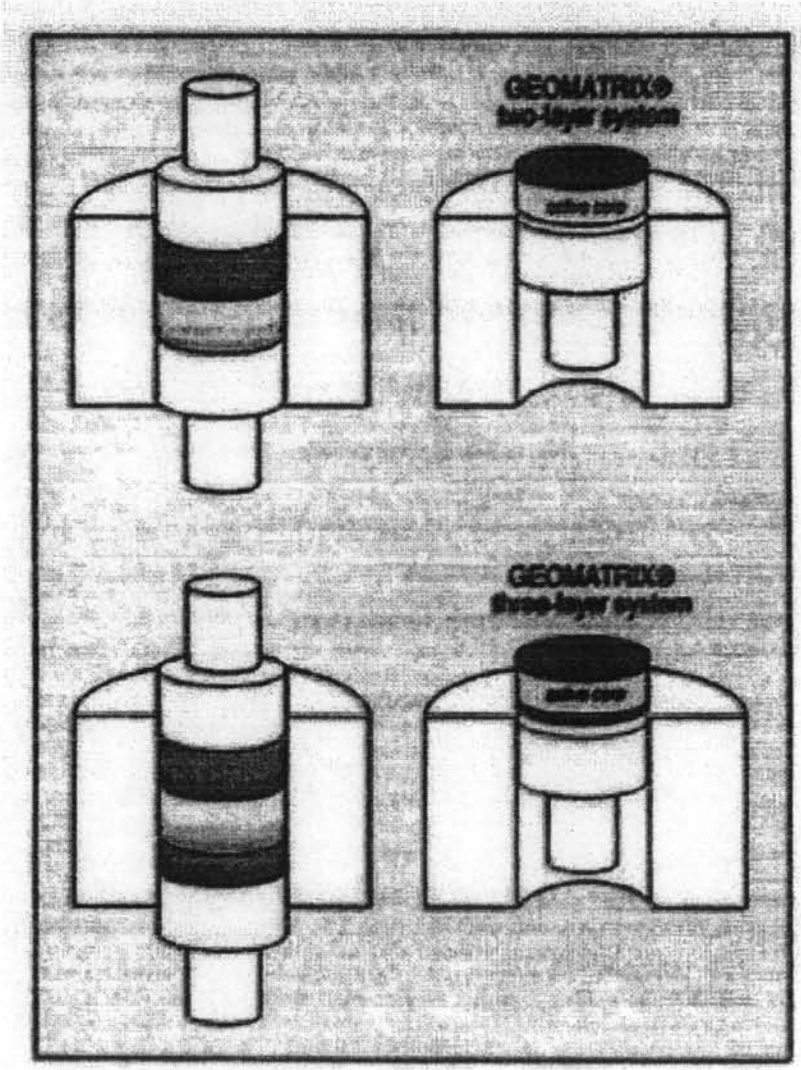

Figure 2.5 Geomatrix® technology: active core plus modulating barriers directly produced during tableting (From Conte and Maggi, 2000)

2.3 Determination of Miscibility of Blend Components by Thermal Analysis

In development of subcutaneous implant drug delivery system, which controls drug release by matrix diffusion, the aims are not only a constant rate of drug release but also a consistent release of drug from the devices. To achieve consistent drug release, uniformity of drug dispersed or dissolved in polymeric matrix is a necessity of the system. Miscibility of drug in the polymer is an important factor indicating the uniformity of drug in the polymeric matrix either molecular dispersion in a dissolved state or regular crystallization in a crystalline state. If drug and polymer are immiscible, lack of the uniformity of drug dispersion and irregular crystallization of drug in the polymeric matrix will occur (Greenhalgh et al., 1999). Furthermore, the variation of drug release from such polymeric matrices will be obtained.

In polymer fields, the miscibility and specific interaction of polymer blends have received much attention because of strong economic incentives arising from their potential applications. Several studies of blends involving one or two polymer components are semicrystalline, which are miscible with several amorphous polymers through hydrogen bonding (Kuo and Chang, 2001; Kuo et al., 2001). This kind of these blends is almost the same as matrix systems containing crystalline drugs dispersed in the polymeric matrices, which have been found in pharmaceutical fields elsewhere (Tantishaiyakul, Kaewnopparat, and Ingkatawornwong, 1996; Satit Puttipipatkhachorn et al., 2001). Moreover, polymer matrices containing amorphous drug dispersions have also been found (Jenquin et al., 1990; Jenquin et al., 1992; Wu and McGinity, 1999; Hülsmann, Backensfeld, and Bodmeier, 2001; Wu and McGinity, 2003). The latter type of matrix systems is likely to amorphous polymer blends. However, the miscibility of drug in polymer matrix has not been determined extensively.

In general, the miscibility of polymer blends can be simply analyzed with differential scanning calorimetry (DSC) to determine whether there are one or two glass transition temperature (T_g) values of those blends. A single T_g point is the most conventionally used criterion for the miscibility of a polymer blend. On the contrary, an immiscible polymer blend exhibits more than one T_g. Over the years, various equations have been offered to predict the variation of the T_g of random copolymers or miscible blends as a function of composition, which can be well interpreted in terms of specific interaction within a polymer blend. The classical equations most used to predict T_g dependence on blend compositions are Gordon-Taylor equation and its modified version equation.

Gordon-Taylor equation has been proposed for the composition dependence of the T_g of compatible polymer blends, which has been derived under the assumption that contacts due to the interaction between the components of the blend are responsible for both conformational arrangement and free volume distribution as well as conformational energy barriers. The probabilities of binary contact are related to the volume fractions of the components, so that the composition dependence of T_g has been related to the volume fractions of the components. The Gordon-Taylor equation

with respect to the volume fraction ($Ø_2$) of the stiffer polymer component (with T_{g2}) has been defined as the following relationship (Schneider, 1988);

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = (1 + K_1)\phi_2 - (K_1 + K_2)\phi_2^{\,2} + K_2\phi_2^{\,3} \qquad 2.10$$

The parameters K_1 and K_2 are related to the difference of the T_g of the polymer components $(T_{g2} - T_{g1})$.

$$K_1 = \frac{K_1^*}{(T_{g2} - T_{g1})} \qquad 2.11$$

and

$$K_2 = \frac{K_2^*}{(T_{g2} - T_{g1})} \qquad 2.12$$

The system-specific constant K_1^* is related to the interaction energy differences between hetero- and homo-contacts, whereas K_2^* considers the energetic effects on the binary contacts of the molecular surrounding.

The ideal behavior of the polymer blend exhibits the equality of the different energetic effects. This means the identical energetic effects of both hetero- and homo-contacts and the equality of the contact energy of the molecular neighborhood. So both K_1^* and K_2^* are equal to zero in the idealized condition of the T_g behavior of compatible polymer blend. The Gordon-Taylor equation resulted in the idealized condition can be expressed;

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = \phi_2 \qquad 2.13$$

$$(T_g - T_{g1}) = \phi_2 T_{g2} - \phi_2 T_{g1}$$

$$T_g = \phi_2 T_{g2} + (1 - \phi_2) T_{g1}$$

Because of $\phi_1 + \phi_2 = 1$, and then

$$T_g = \phi_2 T_{g2} + \phi_1 T_{g1} \qquad 2.14$$

Expressed in terms of the temperature-dependent weight fraction (w_i), the volume fractions ($Ø_i$) are given by the expression;

$$\phi_i = \frac{\frac{\Delta\alpha_i * w_i}{\rho_i}}{\sum_i \frac{\Delta\alpha_i * w_i}{\rho_i}} \qquad 2.15$$

with the density of the components (ρ_i) and the difference between the expansion coefficients of the melt (L) and the glass (gl) at T_{gi} $\left(\Delta\alpha_i = \alpha_{L,i} - \alpha_{gl,i}\right)$.

Introducing equation (2.15) into equation (2.14), Gordon-Taylor equation expressed for the temperature-dependent volume fractions, finally the expression in terms of the temperature-dependent weight fraction can be displayed;

$$T_g = \frac{\rho_2\Delta\alpha_1 w_1 T_{g1} + \rho_1\Delta\alpha_2 w_2 T_{g2}}{(\rho_2\Delta\alpha_1 w_1 + \rho_1\Delta\alpha_2 w_2)} * \frac{\rho_2\Delta\alpha_1}{\rho_2\Delta\alpha_1}$$

Due to $K = \frac{\rho_1\Delta\alpha_2}{\rho_2\Delta\alpha_1}$, so that

$$T_g = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \qquad 2.16$$

The Simha-Boyer rule has indicated that $\Delta\alpha T_g$ is equal to the constant value. Therefore, $\Delta\alpha_i$ can be expressed as;

$$\Delta\alpha_i = \frac{cons\tan t}{T_{gi}}$$

K can be expressed in accordance with the Simha-Boyer rule;

$$K = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \qquad 2.17$$

Using the corrected weight fractions (w_{ic}) in equation (2.16), the corrected weight fraction of component 1 (w_{1c}) is equal to $w_1/(w_1 + Kw_2)$ and the corrected weight fraction of component 2 (w_{2c}) is equal to $Kw_2/(w_1 + Kw_2)$. Thus, equation (2.16) can be rearranged;

$$T_g = w_{1c} T_{g1} + w_{2c} T_{g2} \qquad 2.18$$

$$T_g = (1 - w_{2c}) T_{g1} + w_{2c} T_{g2}$$

$$T_g - T_{g1} = (T_{g2} - T_{g1}) w_{2c}$$

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = w_{2c}$$

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = w_{2c} = \frac{Kw_2}{w_1 + Kw_2}$$

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = \frac{Kw_2}{(1 - w_2) + Kw_2}$$

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = \frac{Kw_2}{1 + (K - 1)w_2} \qquad 2.19$$

Equation (2.19) can be linearized in order to determine the fitting constant *K*. The resulting equation is;

$$\frac{T_{g2} - T_g}{T_g - T_{g1}} = \left(\frac{1}{K}\right)\left(\frac{1 - w_2}{w_2}\right) \qquad 2.20$$

The fitting constant *K* is obtained from the slope of the plot between $(T_{g2} - T_g)/(T_g - T_{g1})$ and $w_2/(1 - w_2)$. It means that the fitting constant *K* can be expressed in terms of the weight fraction of component 2 (w_2).

In terms of the corrected weight fraction of component 1 (w_{1c}), equation (2.18) can be expressed;

$$T_g = w_{1c}T_{g1} + (1 - w_{1c})T_{g2}$$

$$T_g - T_{g2} = (T_{g1} - T_{g2})w_{1c}$$

$$\frac{T_g - T_{g2}}{T_{g1} - T_{g2}} = w_{1c}$$

$$\frac{T_g - T_{g2}}{T_{g1} - T_{g2}} = w_{1c} = \frac{w_1}{w_1 + Kw_2}$$

$$\frac{T_g - T_{g2}}{T_{g1} - T_{g2}} = \frac{w_1}{w_1 + K(1 - w_1)} * \frac{\frac{1}{K}}{\frac{1}{K}}$$

$$\frac{T_g - T_{g2}}{T_{g1} - T_{g2}} = \left(\frac{1}{K}\right) * \frac{w_1}{1 + \left[\left(\frac{1}{K}\right) - 1\right] w_1}$$

$$\frac{T_{g2} - T_g}{T_{g2} - T_{g1}} = \left(\frac{1}{K}\right) * \frac{w_1}{1 + \left[\left(\frac{1}{K}\right) - 1\right] w_1} \qquad 2.21$$

Equation (2.21) can be linearized in order to evaluate the fitting constant K. The resulting equation is;

$$\frac{T_g - T_{g1}}{T_{g2} - T_g} = K * \frac{(1 - w_1)}{w_1} \qquad 2.22$$

The fitting constant K is obtained from the slope of the plot between $(T_g - T_{g1})/(T_{g2} - T_g)$ and $(1 - w_1)/w_1$. It means that the fitting constant K can be expressed in terms of the weight fraction of component 1 (w_1). From equation (2.20) and (2.22), their slopes are directly related with each other via the fitting parameter K. The slope of equation (2.20) in terms of w_2 is identical with the reciprocal slope of equation (2.22) in terms of w_1. This is the Gordon-Taylor behavior.

In the case of polymer blends exhibiting behavior deviating from an ideal behavior, the slope of equation (2.20) in terms of w_2 is quite different from the reciprocal slope of equation (2.22) in terms of w_1. It means that the fit of Gordon-Taylor equation to experimental data fails. This suggests an interaction contribution to the Gordon-Taylor parameters. The Kwei equation is recommended in this case. The Kwei relation is identical to a second-order equation of the proposed model expressed in equation (2.10). It considers different energetic effects of the binary contact ($K_1 \neq 0$), but neglects the effects of the immediate neighborhood of contacts ($K_2 = 0$). Therefore, equation (2.10) can be written under this assumption as shown below;

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = (1 + K_1)\phi_2 - K_1 \phi_2^{\,2}$$

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = (1 + K_1) w_{2c} - K_1 w_{2c}^{\,2} \qquad 2.23$$

$$T_g - T_{g1} = (T_{g2} - T_{g1}) w_{2c} + (T_{g2} - T_{g1})\left[K_1 (w_{2c} - w_{2c}^{\,2})\right]$$

$$T_g = (1 - w_{2c}) T_{g1} + w_{2c} T_{g2} + (T_{g2} - T_{g1})\left[K_1 w_{2c} (1 - w_{2c})\right]$$

$$T_g = w_{1c} T_{g1} + w_{2c} T_{g2} + (T_{g2} - T_{g1})(K_1 w_{2c} w_{1c}) \qquad 2.24$$

Substituting $w_{1c} = w_1/(w_1 + Kw_2)$ and $w_{2c} = Kw_2/(w_1 + Kw_2)$ in equation (2.24);

$$T_g = \frac{w_1 T_{g1} + Kw_2 T_{g2}}{w_1 + Kw_2} + (T_{g2} - T_{g1}) \frac{K_1 K w_2 w_1}{(w_1 + Kw_2)^2} \qquad 2.25$$

$$q = (T_{g2} - T_{g1}) \frac{K_1 K}{(w_1 + Kw_2)^2} \qquad 2.26$$

Introducing equation (2.26) into equation (2.25), so that Kwei equation can be obtained as expressed in the following equation;

$$T_g = \frac{w_1 T_{g1} + Kw_2 T_{g2}}{w_1 + Kw_2} + q w_2 w_1 \qquad 2.27$$

The Kwei equation or the second order equation of the proposed model as expressed in equation (2.23) can be linearized in a similar manner as the Gordon-Taylor equation but it can be assumed a first approximation of the quadratic term in w_{2c} to be negligible. Then, the respective equations are in terms of w_{2c};

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} \approx (1 + K_1) w_{2c} \qquad 2.28$$

and in terms of w_{1c};

$$\frac{T_{g2} - T_g}{T_{g2} - T_{g1}} \approx (1 + K_1) w_{1c} \qquad 2.29$$

The linearized equations corresponding to equation (2.28) and (2.29) are;

$$\frac{T_{g2} - T_g}{T_g - T_{g1}} = \frac{-K_1}{1 + K_1} + \frac{1}{K(1 + K_1)} * \frac{1 - w_2}{w_2} \qquad 2.30$$

and

$$\frac{T_g - T_{g1}}{T_{g2} - T_g} = \frac{-K_1}{1 + K_1} + \frac{K}{1 + K_1} * \frac{1 - w_1}{w_1} \qquad 2.31$$

It is evident that the slopes of the linearized equations are no more directly related with each other. This behavior is different from the Gordon-Taylor behavior. The Kwei parameter is the Gordon-Taylor parameter (K) including an interaction contribution (K_1).

From equation (2.30) and (2.31) an interaction contribution from the homo- and hetero-contacts in compatible polymer blends (K_1) can be obtained from the intercept and the Gordon-Taylor parameter (K) can also be obtained from the slope. The K and K_1 are the important keys for calculation of the q parameter via equation (2.26). The q parameter is a parameter reflecting the balance between breaking the intra bonding and forming the inter bonding. Normally q parameter corresponds to the strength of hydrogen bonding. The q value of the polymer blend should depend on an entropy change corresponding to the change in the number of hydrogen bonding interactions. In the case of negative q value, it indicates that the self-associated hydrogen bonding is stronger than the inter-associated hydrogen bonding. In reciprocal way, the positive q value indicates that the self-associated hydrogen bonding is weaker than the inter-associated hydrogen bonding. The higher q value, the stronger hydrogen bonding (Kuo and Chang, 2001; Kuo et al., 2001).

The third order equation of the proposed model considers the contact interaction energies ($K_1 \neq 0$) and the influence of the molecular neighborhood on the contact energy ($K_2 \neq 0$), so that equation (2.10) can be written in terms of the corrected weight fraction of the stiffer polymer (w_{2c}) as displayed below;

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = (1 + K_1)w_{2c} - (K_1 + K_2)w_{2c}^{\ 2} + K_2 w_{2c}^{\ 3} \qquad 2.32$$

The equation (2.32) can be resolved for the T_g of the blend as the following expression;

$$T_g = \frac{(1-w_2)T_{g1} + Kw_2T_{g2}}{1+(K-1)w_2} + \frac{K_1^{*}K}{[1+(K-1)w_2]^2} * (1-w_2)w_2 - \frac{-K_2^{*}K_2}{[1+(K-1)w_2]^3} * (1-w_2)w_2^{\ 2} \qquad 2.33$$

Equation (2.33) is an extended Gordon-Taylor equation, which is written in terms of the weight fraction of the stiffer polymer (w_2). Due to equation (2.11) and (2.12), K_1^{*} and K_2^{*} are related to K_1 and K_2, respectively, so that the influence of the weight fraction of the components on the T_g is included both K_1 and K_2.

In the case of a crystalline polymer blended with an amorphous polymer, the melting point depression of a crystalline polymer in blend provides important information about its miscibility and its associated polymer-polymer interaction parameter. An immiscible or partially miscible blend typically does not show the depression of melting point whereas a miscible blend displays the melting point depression when increasing the content of amorphous polymer. The temperature reduction is caused by morphological effects and thermodynamic reasons (Kuo and Chang, 2001; Kuo et al., 2001). In a thermodynamically miscible blend, the amorphous polymer resides inside the interlamellar regions of the semi-crystalline polymer. It expands the interlamellar regions. The spherulite radial growth rate, time to half volume crystallization and melting temperature of semi-crystalline component generally decrease as the concentration of the amorphous polymer increases. The mean field self-consistent theory to model the crystallization of blends containing di-block copolymers in which one of the copolymer blocks is crystallisable and the other

is amorphous has been proposed. The expression based on this theory for the free energy can be interpreted as a sum of free energy of the free crystalline block, the amorphous block and entropy and enthalpy of interactions between the two blocks. For long chain polymers, the effect of the end groups has been ignored. The change in partial free energy of the crystals in a miscible blend (Δg_{2b}) can be expressed by (Rostami, 2000);

$$\Delta g_{2b} = \Delta g_2 + \Delta g_m \qquad 2.34$$

where Δg_2 is the change in partial free energy of crystalline unit of the homopolymer and Δg_m is the change in partial free energy of mixing.

The equilibrium melting temperature is defined as the last temperature that infinitely long crystal melts. By definition, at the equilibrium melting temperature of the blends, where the last crystal melts, Δg_{2b} becomes zero, so that equation (2.34) can be expressed as followed;

$$0 = \Delta g_2 + \Delta g_m$$

$$\Delta g_2 = -\Delta g_m$$

$$\Delta h_2 - T_{mb}\Delta S_2 = -\Delta g_m$$

$$1 - \frac{T_{mb}\Delta S_2}{\Delta h_2} = \frac{-\Delta g_m}{\Delta h_2} \qquad 2.35$$

where Δh_2 is the heat of fusion of a crystalline polymer, T_{mb} is the equilibrium melting point of a blend, and ΔS_2 is the entropy of crystalline unit in a blend.

In condition of a narrow temperature range between T_{mb} and T_m, which is the equilibrium melting point of a crystalline polymer, it is reasonable to assume that Δh_2 and ΔS_2 are temperature independent hence;

$$T_m = \frac{\Delta h_2}{\Delta S_2} \qquad 2.36$$

Introducing equation (2.36) into equation (2.35), so that equation (2.35) can be expressed as followed;

$$1 - \frac{T_{mb}}{T_m} = \frac{-\Delta g_m}{\Delta h_2} \qquad 2.37$$

$$T_m - T_{mb} = T_m * \left(\frac{-\Delta g_m}{\Delta h_2} \right)$$

$$T_{mb} = T_m + T_m * \left(\frac{\Delta g_m}{\Delta h_2} \right)$$

$$T_{mb} = T_m * \left[1 + \left(\frac{\Delta g_m}{\Delta h_2} \right) \right] \qquad 2.38$$

A popular equation for Δg_m is given by the classic Flory-Huggins mean field model. When the crystalline polymer is designated as the second component in the mixture, the lattice model gives;

$$\Delta g_m = \frac{RT_{mb}V_2}{V_1} \left[\ln\left(\frac{\phi_2}{r_2}\right) + \left(\frac{1}{r_2} - \frac{1}{r_1}\right)\phi_1 \right] + \frac{RT_{mb}V_2}{V_1} \lambda_{21}\phi_1^{\,2} \qquad 2.39$$

where Ø is the volume fraction and r is the chain length of each component denoted by the subscript used. V_1 and V_2 are the molar volume of the amorphous unit and the crystalline unit, respectively. χ_{21} is the polymer-polymer interaction parameter. R is the universal gas constant. T_{mb} is the temperature of the blends. The term in the square bracket represents contribution from the combinatorial entropy to the chemical potential changes per mole of crystalline unit in the mixture. As a major contribution to the molar free energy changes of mixing is provided by the enthalpic term, which is the second term of equation (2.39), the entropic contribution is neglected. The Δg_m can be written in term of an approximate chemical potential form as displayed;

$$\Delta g_m = \frac{RT_{mb}V_2}{V_1} \lambda_{21}\phi_1^{\,2} \qquad 2.40$$

Substituting this approximated term into equation (2.37) and rearranging, so that the resulting relationship is given as shown below (Rostami, 2000; Pimbert, Avignon-Poquillon, and Levesque, 2002);

$$1 - \frac{T_{mb}}{T_m} = \frac{-RT_{mb}V_2}{\Delta h_2 V_1} \lambda_{21}\phi_1^{\,2}$$

$$\frac{1}{T_{mb}} - \frac{1}{T_m} = \frac{-RV_2\lambda_{21}\phi_1^{\,2}}{\Delta h_2 V_1} \qquad 2.41$$

χ_{21} can be written as the following expression (Nishi and Wang, 1975; Kuo and Chang, 2001);

$$\lambda_{21} = \frac{BV_1}{RT_{mb}} \qquad 2.42$$

where B is the interaction energy density characteristic of the polymer pair. Substitution of equation (2.42) into equation (2.41) yields the Nishi-Wang equation (Nishi and Wang, 1975; Kuo and Chang, 2001; Kuo et al., 2001) displayed as the resulting expression;

$$\frac{1}{T_{mb}} - \frac{1}{T_m} = \frac{-RV_2\phi_1^{\,2}}{\Delta h_2 V_1} * \frac{BV_1}{RT_{mb}}$$

$$\frac{1}{T_{mb}} - \frac{1}{T_m} = \frac{-BV_2\phi_1^{\,2}}{\Delta h_2 T_{mb}}$$

$$1 - \frac{T_{mb}}{T_m} = \frac{-BV_2\phi_1^{\,2}}{\Delta h_2}$$

$$T_m - T_{mb} = \frac{-T_m BV_2\phi_1^{\,2}}{\Delta h_2} \qquad 2.43$$

Gordon-Taylor equation, Kwei equation and Nishi-Wang equation have ordinarily been used to describe the miscibility of polymer blends. However, the utilization of these equations in order to describe the miscibility of drug in polymeric matrices has not extensively been found.