CHAPTER II
THEORETICAL BACKGROUND AND LITERATURE REVIEW

2.1 Transdermal Drug Delivery System

Transdermal drug delivery system (TDDS) is designed to deliver a therapeutically effective amount of drug across a patient's skin. In the first-generation, TDDS is responsible for most of the transdermal patches using in clinics which are suitable for delivery of low-molecular weight drugs, lipophilic, and efficacious at low doses. Limitation of this generation is the barrier presented by skin's outermost layer, the stratum corneum (Prausnitz and Langer, 2008).

Second-generation TDDS has been developed to enhance the skin's permeability. The improvement methods, such as conventional chemical enhancers, iontophoresis, and noncavitational ultrasound contain are composed of:

(i) disturbing stratum corneum structure
(ii) supplying an driving force for transport into the skin
(iii) keeping away from harm to deeper, living tissues.

As a result, this generation has higher clinical practice by improving small-molecule delivery for localized, dermatological, cosmetic, and some systemic applications, however it has provided little for the delivery of macromolecules.

For the third-generation TDDS, their aim is not only to powerfully disrupt the stratum corneum barrier, but also to protect deeper tissues. Electroporation, microneedles, thermal ablation, microdermabrasion, and cavitational ultrasound are the way to deliver macromolecules and vaccines.

2.2 Methods of Controlled Drug Release

2.2.1 Temporal Control

This method delivers the drug over an extended duration or at a specific time during treatment, which is highly preferred for drugs that are rapidly metabolized and eliminated from the body after organization.

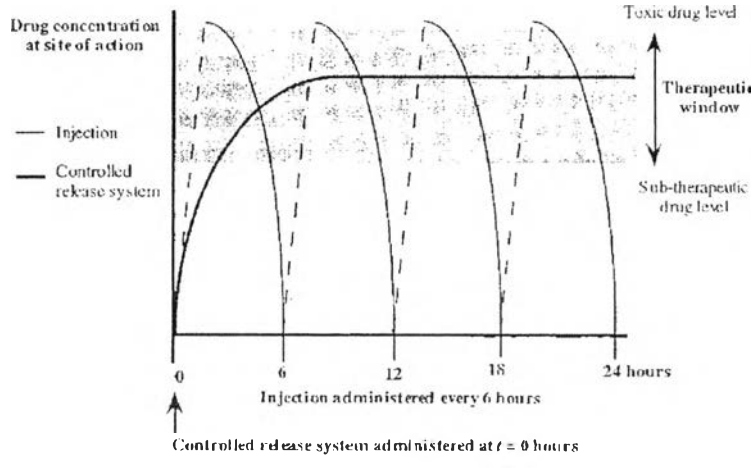


Figure 2.1 Drug concentrations at site of therapeutic action after delivery as an injection (thin line) and as a temporal controlled release system (bold line) (Uhrich, *et al.*, 1999).

According to Figure 2.1, it shows the fluctuation of drug concentration during the 24 h period after injecting the drug and the therapeutic window (i.e., the concentration of drug that has no dangerous side effects and gives benefit effects), which is only a portion of the treatment period. With the controlled release system, the rate of drug release equals the rate of drug elimination, so the drug concentration is in the therapeutic window for the large majority of the observation period (Uhrich *et al.*, 1999).

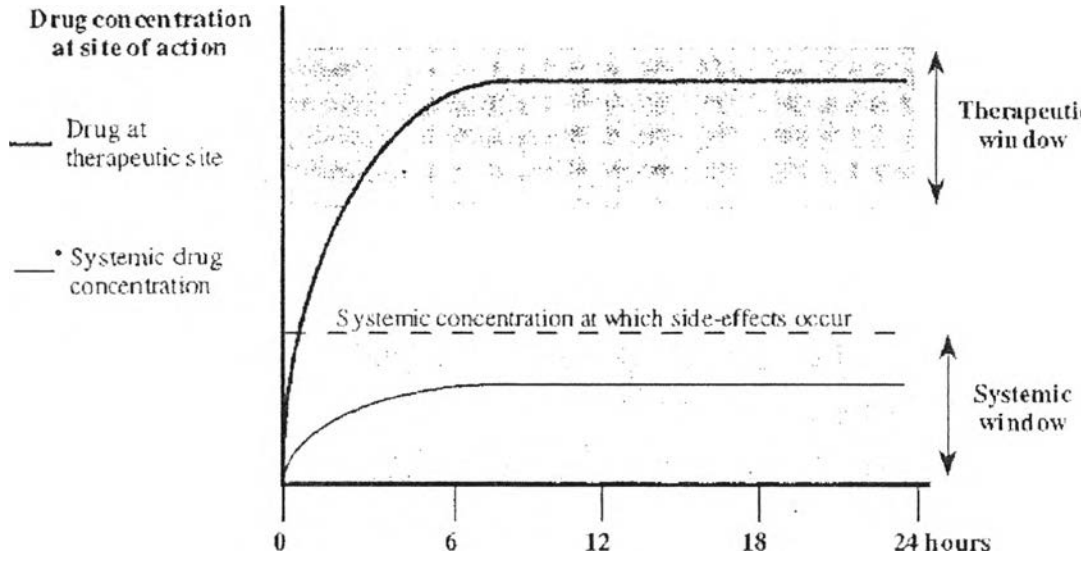


Figure 2.2 Drug delivery from an ideal distribution controlled release system. Bold line: Drug concentrations at site of therapeutic action. Thin line: systemic levels in which side effects occur (Uhrich, *et al.*, 1999).

2.2.2 Distribution Control

The advantage of this control is shown in Figure 2.2. There are two principle situations, the first is when the natural distribution causes drug molecules to encounter tissues and cause major side effects that prohibit further treatment. This situation is often the cause of chemotherapy failure when bone marrow cell death prevents the patient from undergoing a complete drug treatment. The second situation is when the natural distribution of the drug does not allow drug molecules to reach their molecular site of action. For example, a drug molecule that acts on a receptor in the brain will not be active if it is distributed by the patient's blood system but cannot cross the blood-brain barrier (Uhrich *et al.*, 1999).

Roseman (1972) studied the *in vitro* releases of four progesterone-type steroids as four types of drug from a silicone polymer. The four types of drug namely progesterone, medroxyprogesterone acetate, 6α-methyl-11β-hydroxyprogesterone and 17α-hydroxyprogesterone. Progestone was released at the fastest rate and 17α-hydroxyprogesterone was released at the lowest rate because the release of steroids depended on molecular structure. The diffusion coefficient depended on the presence of filler particles within the polymer which was related to

the formation of voids and the size of voids. The high diffusion coefficient was attributed to the release of hold formation because of a high internal chain mobility within the silicone polymer. Adding the filler into the silicone polymer decreased the amount of drugs release because of the adsorption of drugs onto the filler. The filler had little effect on progesterone and metdoxyprogesterone acetate because two steroids were highly soluble.

Sharma *et al.* (1988) studied the controlled release devices of the two-phase morphology of block copolyurethane. Prednisolone was used as a drug which was released from the copolyurethane devices. Copolyurethane devices were prepared by the solution casting method and the swelling method. The lower release rates were from the solution casting devices because of the high intermolecular interaction force between prednisolone and the urethane chain of the co-polyurethane. The devices by the swelling method allowed a higher release rate because the interactions of intermolecular between prednisolone and the urethane chain of the co-polyurethane were absent.

Sintov *et al.* (1988) studied the formulation of a lidocaine-polyuretane matrix to improve the release property and the implanting of drug delivery system into the arrhythmic epicardium. Lidocaine was used as a drug. Polyurethane matrixes were prepared by three ways via film casting with or without stirring and compression molding and sealing. From the results, matrices formulated with the compression molding were the highest drug release rate. The results of SEM micrographs showed the morphology of all matrices before and after released which affected the released rate. Because stirring of the polymer during the formulation enhanced reactive crosslinking so it generated cavities during the polymerization. However, the compression molding reduced these cavities and limited the releasing surface by bending of impermeable sheeting.

Carelli *et al.* (1989) studied the method to promote the macromolecule (protein) released rate from a polydimethylsiloxane elastomer as a matrix. The macromolecule was brovine serum albumin (BSA) and soldium chloride (NaCl) in volume ratio of 35:65 or 70:30. The releasing of protein depended on the solubility of granule BSA-NaCl and the cracking of polymer matrix. The releasing of protein

was from the solute traveled along the aqueous pathways in the matrix. The NaCl flux was faster than BSA because NaCl had higher diffusivity.

Golomb *et al.* (1990) studied the characteristic between drug particle size, release rate, and swelling property of a silicone elastomer. Both types of silicone elastomer studied were silastic 382 and silastic Q7. The model drug was potassium dichromate (PDC). The PDC was dispersed into the silastic 382 and then the catalyst was added. Silastic Q7 was prepared by keeping under vacuum at 0.07 Torr for 30 min. The release rate and swelling property of silastic 382 increased with decreasing drug particle size because the increasing of surface area for dissolution and pores increased in the matrices. Increasing drug particle size increased release rate and decreased swelling property of matrices because air bubbles were trapped in the silastic Q7matrices from fabrication when the large drug particle size was used because more pores were present.

Rao and Diwan (1997) studied drug permeability from cellulose acetate (CA) free film with using dibutylphthalate (DBP), polyethylene glycol 600 (PEG 600), and propylene glycol (PG) as plasticizers. The plasticizers were used to prepare the CA free film at a concentration of 40 %wt of dry polymer weight. Diltiazem hydrochloride (DLT) and indomethacin (IN) were used as drugs for the permeation study. Keshary-Chein diffusion cell was used to study drug diffusion and permeability. The PBS (pH 7.4) was used as the receptor fluid and controlled temperature of buffer by circulated water around the receptor compartment at 37 °C. For the permeation study, 10 ml (2 %w/v) of drug solution was poured into the donor compartment. The drug content was measured by using UV-visible spectrophotometer at wavenumber 236 nm and 318 nm for DLT and IN, respectively. The drugs diffusion was followed zero order kinetic. The permeability of both drugs increased with increasing the amount of plasticizer. The CA free film with PEG 600 showed the highest amount of drugs permeation due to the formation of small pores.

Ramanathan and Block (2001) studied the characteristics of chitosan gel as a matrix for using in drug delivery application. The chitosan gel was prepared by acetylation of chitosan. In this work, hydrocortisone (HY), benzoic acid (BA), and lidocaine hydrochloride (LH) were used as drugs. HY, BA, and LH were neutral,

anionic, and cationic drug, respectively. The amount of drugs release from chitosan gels were ranked as follow BA>HY>LH. The electro-kinetic phenomena affected to the drugs release behavior. BA was of the highest releasing rate due to the electro-repulsive force under applied electrical potential. Hence, it enhanced the mobility of BA molecule from the gel. LH was of the lowest releasing rate under applied electrical potential due to the electro-attractive force of LH molecule and the collapse of the gel.

Gondaliya and Pundarikakshudu (2003) studied the bupropion permeation by using Eudragit as the adhesive and rate controller polymer matrix. Triethylcitrate (TEC) and DBP were used as plasticizers. Propylene glycol, myristic acid, and succinic acid were used as releasing modifiers. The transdermal adhesive patch was prepared by a casting method. Drug permeation was studied by using a Franz diffusion cell. The bupropion release was increased with increasing concentration of bupropion due to the increasing of concentration gradient across the skin. The release of drug followed by zero order release kinetic which explained by Higushi's equation. The effect of TEC and DBP did not improve the drug permeation. The presence of propylene glycol and myristic acid in the adhesive matrix improved the drug permeation due to the difference in thermodynamic activity and the solubility of free base in the matrix. The succinic acid decreased the drug permeation because the adhesive matrix became rigid due to the crosslinking by succinic acid. The bupropion release amount increased by nearly 4 times (from 41.2 to 1301 mg) with increasing the matrix size by 4 times (from 3.14 to 12.56 cm^2). These results showed the improvement of drug permeation by increasing the drug concentration in the matrix and the drug size of the matrix.

Guoqiang *et al.* (2007) studied the effect of the surfactants on the lifetime of aqueous path ways by determining the electrical features of the hairless mice skin. Sodium dodecanesulphonate (SDS) and Tween 80 were used as surfactants. This experiment studied the effect of the surfactants on transport of piroxican (PIX) as a drug. The sample was prepared by placing the mouse skin between the two compartments, one the donor compartment and another receiver compartment. The area of sample was 0.4 cm^2 and tested at 37 °C, which was controlled by cycling water. The PBS at pH 7.4 was used as the buffer solution

where the donor compartment was filled with PBS or PIX. For the result, the electric field created the aqueous pathways in the lipid layers and SDS increased electrical conductivity of the solution, thus, the skin resistance dropped to a low level after applying electric field. Hence, the shrinkage of the electro pores was hindered. SDS retarded the recovery of skin resistance the similar to the phenomena of Tween 80. The charge of SDS was faster than Tweed 80 under electric field. However, a higher concentration of the surfactants let to a higher transdermal flux.

Juntanon *et al.* (2008) studied electrically controlled drug delivery by using poly(vinyl alcohol) (PVA) as the matrix/carriers. Sulfosalicylic acid (SSA) and glutaradehyde were used as an anionic model drug and a crosslinking agent, respectively. The drug-loaded PVA hydrogels were prepared via solution-casting method. Acetate buffer pH 5.5 at temperature 37 °C was used as the buffer solution during a permeation study period for 48 h. From the results of the amount of drug permeation under effects of crosslinking agent, the molecular weight between crosslink, and the mesh size of the PVA hydrogels were larger at lower crosslinking ratios. Under applied electric field on the PVA hydrogel, the mesh sizes were expanded. The amount of drug released from the PVA hydrogels increased with decreasing the amount of crosslink ratio. However, increasing electric field was increased the amount of released drug because of a larger mesh size of PVA hydrogel and a higher electrostatic force driving negatively charged drug through the polymer matrix. Moreover, the electric field could create the transient microspores in the liophilic stratum corneum in the pigskin to obtain an easier way to transport drug.

Chansai *et al.* (2009) synthesized a conductive polymer and blended with hydrogel that used sulfosalicylic acid (SSA) as an anionic model drug. SSA doped polypyrrole (PPy) as a carrier, and poly(acrylic acid) (PAA) as a matrix. PAA film and the blended film were prepared via solution casting using ethylene glycol dimethacrylate (EGDMA) as a crosslink agent. Diffusion studies were investigated by using the modified Franz diffusion cells for the *in vitro* studies. Acetate buffer was used as a buffer solution at pH 5.5 and the temperature at 37 °C. From the result, SSA doped PPy had higher electrical conductivity than undoped PPy because SSA doped PPy possessed higher amount of charge carriers, degree of crystallinity, and charge mobility. The mesh size of hydrogel was the main factor for the releasing of

drug. An increase in the crosslinking agent used the mesh size was smaller and the release of drug was decreased. However, electric-field generated the electrostatic force which drove the drug to the oppositely charged electrode.

Niamlang and Sirivat (2009) investigated a combined conductive/hydrogel as a controlled drug release device using salicylic acid (SA) as an anionic model drug, poly(p-phenylene vinylene) (PPV) as a conductive polymer and polyacrylamide (PAAM) as a hydrogel matrix with N,N-MBA as the crosslinking agent. SA-doped PPV was prepared by the acid-assisted redox doping reaction. The samples were placed on the top of acetate buffer solution (pH 5.5 at 37 °C) that was stirred throughout the experiment period (48 h.). The lower amount of crosslinking agent resulted in a larger pore size of hydrogel so the amount of SA release from the SA-loaded PAAM was higher at any given time. Under higher electric field, the amount of SA released occurred at a higher rate because the driving force between the negatively charged drug molecule and the negatively charged electrode was higher. Electrostatic force pushed the negatively charged drug through the hydrogel matrix and the PPV chain also expanded so it generated a larger free volume to facilitate the drug release.

Im *et al.* (2010) studied an eletro-sensitive TDD by an electrospinning method. Polyethylene oxide and pentaerythritol triacrylate polymer was used as the matrix and multi-walled carbon nanotubes (MWNTs) were used as additive for increasing the electrical sensitivity. The amount of drug released increased with higher applied electric field and the amount of drug released was much higher with MWNTs loading because of the higher conductivity of the sample from the electrical network present. The released drug depended on the swelling of the sample. The fiber was swelled so it attributed to swelling of the crosslinked polymer.

Argemi *et al.* (2011) studied the characteristic of transdermal patch with prepared by using ethylene vinyl acetate and Eudragit® E100 blended. Naproxen was used as the drug impregnated inside the polymer matrix. Naproxen was transferred inside the polymer matrix by soaking the polymer matrix under 1000 psi of CO_2 to obtain porousity on the matrix surface. Then, naproxen solution (1 %wt) was placed in contact with the polymer matrix and CO_2 was applied into the system. Naproxen was successfully impregnated inside the polymer matrix. The

release apparatus was studied by using a Franz diffusion cell with nylon membrane of 0.45 μm pore size. The PBS buffer was used as the buffer solution in the receptor compartment with various pH values of 6.8 and 7.4. The drug diffusion was higher using the PBS buffer of pH 7.4. The drug release characteristic was considered by drug delivery kinetic that showed rapidly release rate in the first 6 h, and then the releasing rate decreased up to 24 h. As the drug concentration was decreased, the drug delivery rate also decreased.

Paradee *et al.* (2012) studied effects of crosslinking-ratio, model drug, and applied electric field on the controlled release behavior of calcium-alginate hydrogel (Ca-Alg). The Ca-Alg was prepared by solution casting using $CaCl_2$ as a crosslinking-agent. Benzoic acid (BA) and tannic acid (TA) were used as anionic model drugs and folic acid (FA) was used as a cationic model drug. The drug diffusion coefficient decreased with increasing crosslinking ratio because of a smaller pore size of hydrogel. The BA was the highest among of release rate because BA had the smallest size of drug molecule. However, the TA was the lowest amount released because of the biggest size of drug molecule. The effect of electric field strength from the negatively charged electrode was to retard the amount and released rate of FA whereas increased the amount of released rate of BA and TA because the positive charged FA generated the attractive force with the negatively charged electrode.

Thorngkham *et al.* (2015) studied amount of IN permeation under effects of electrical potential and crosslinking ratio. The IN was loaded into polycarbazole (PCz) which was a conductive polymer to enhance the permeation efficiency of IN through pig skin. The Franz diffusion cell was used in the IN permeation study. Amount of IN permeation decreased when increasing crosslinking ratio because the higher crosslinking ratio provided smaller pathway and retarded the permeation of drug through the matrix. The amount of IN permeation from IN-loaded DCNR film increased with increasing electrical potential due to the electro-repulsive force between the negatively charged drug molecule and the negatively charged electrode. IN-doped PCz/DCNR film possessed a higher amount of IN permeation under applied electrical potential than IN-loaded DCNR film because the electrical potential provided a stronger reduction reaction between IN and PCz.

2.3 Natural Rubber

Natural rubber (NR) is one of renewable raw materials obtained from the latex of several plants, but the only important commercial source is the tree *Heveabrasiliensis* in which contains 30–35% rubber. The latex is stabilized with ammonia after collection and transported to a plant where it is continuously centrifuged to gain higher rubber percentage which around 60% rubber. The structure of *cis* 1, 4-polyisoprene is shown in Figure 2.3.

Sakdapipanich and Rojruthai (2012) stated that a latex can be classified by the employed chemicals and processes.

1. High-ammonia (HA) is the addition of ammonia which is not less than 0.6% into the latex to have a long-term protection of concentrated latex.
2. Low-ammonia (LA) includes 0.2–0.3% ammonia, zinc oxide (ZnO), tetramethylthiuram disulfide (TMTD) as a bactericide, and other necessary additives to preserve concentrated latex.
3. Double centrifuged (DCNR) is highly purified latex prepared by re-centrifuging the first centrifuged latex to enhance a separation of the non-rubber components from the rubber. The double centrifuged latex is generally very stable and has good storage properties.
4. Deproteinized natural rubber (DPNR) is the latex with proteins removed to prevent type I allergic by using a proteolytic enzyme in the presence of surfactants. The physical properties of deproteinized natural rubber are almost equivalent to those of regular natural rubber. Moreover, the dynamic properties are also improved leading to the increase rubber hydrocarbon content.

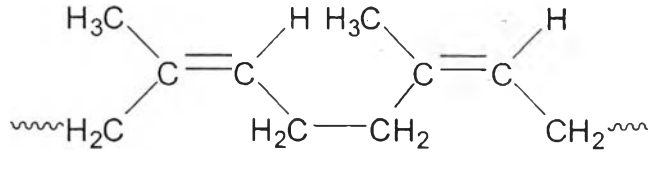


Figure 2.3 The structure of cis 1, 4-polyisoprene.

Geer (1922) studied the developments of the rubber. The important physical properties were mechanical, the action of temperature and time which improved by vulcanization method. To attain highest values of vulcanization under operation, several mixtures had been studied during the past few years.

Natural rubber (NR) had been used for transdermal drug delivery system. For example, Healy *et al.* (1999) studied the release of saponin from a NR matric where Calendula officinal is as a source of sustained molluscicidal saponin. The rubber was prepared by a vulcanization method. The fillers (high abrasion furnance black (HAF) and hydrate silica (Hisil)) were added for improving mechanical properties. The release rate of saponin increased with increasing plant concentration and the highest amount of saponin release was observed first and then the steady state was observed. In the first day, the free particles of saponin were not physically bonded with the matrix and the blooming phenomenon resulted. The presence of the filler retarded the amount of saponin released. The amount of saponin released from the formulation containing HAF was higher than containing Hisil because the particle size of HAF was larger than Hisil. The amount of saponin released increased as temperature increased from 25 to 65 °C because the relaxation of rubber chain helped water to penetrate inside the matrix and pulled the saponin out.

Herculano *et al.* (2009) studied natural rubber latex (NLR) membranes as a protein delivery system by *in vitro* protein delivery experiment. Different polymerization temperatures (-10 to 27 °C) were used to control the membranes morphology. The protein released was affected by the morphology of the membranes with pores size and number of pores. The density of pores was higher as polymerization temperature decreased. The protein released from the membranes polymerized at room temperature was the highest (compared with the membranes polymerized at -1 and -10 °C). The membrane polymerized at room temperature was with no pore because the chains were organized during polymerization so the formation of pores was correlated with a higher cross-linking.

Herculano *et al.* (2010) studied different polymerization of NRL conditions in order to control the metronidazole (MET) release. The MET was used as a model drug released from NRL by using different manufacturing processes. The NRL was prepared at different temperatures for polymerization (-100, -10, room temperature

(RT), and 40 °C) and the MET released was investigated by the UV-visible method. The different polymerization temperatures showed different pore sizes and density values where at RT and 40 °C did not yield pore. However, the density of pores increased when the polymerized temperature decreased. The MET released was a function of time and at -100 °C was higher. The slower releases of MET were due to the MET diffusing slowly through the matrix because of the amount of encapsulated material on the surface (as a reservoir) and the crosslinking density which induced the release rate to become slower.

Riyajan *et al.* (2012) studied the NRL grafting with modified cassava starch (ST), with potassium persulfate (KSO) as a catalyst, to be used as a polymer membrane for encapsulating fertilizer (urea). The swelling behavior was investigated that can affect the urea releasing behavior. The modified ST was prepared by mixing KSO with gelalinized ST and then NR was added in modified ST. The mixture was casted on a glass plate at room temperature for 3-4 days. The swelling ratio of NR/ST blend without KSO showed the highest value because of the absence of chemical interaction between NR and ST. The swelling ratio of NR-g-ST decreased because of the grafting of ST on NR. However, the swelling ratio of NR-g-ST increased with increasing ST contents because of its hydrophilic property of ST. NR-g-ST was a core-shell structure while hydrophilic starch part and the urea particle were encapsulated inside the matrix. The released urea was under swelling phenomenon that the wall was broken by solvent action and hydrolysis.

Deproteinized natural rubber (DPNR) is interesting to use in many applications because the protein in NR causes the skin allergic. The protein in NR can be removed in many ways. Perrella and Gaspari (2002) studied and compared properties of DPNR with various methods for producing the medical glove. The DPNR methods were centrifugation, post washing, and enzyme treatment of natural rubber (ET-NRL). ET-NRL showed the most suitable method to produce medical glove because ET-NRL could be used for large scale production with good mechanical, aging, and barrier properties. The protein content was removed during the DPNR process. Hence, the stability of DPNR decreased because the protein helped to maintain the latex colloidal stability during collection. The problem was caused by the coagulation of rubber latex. Ammonia was usually added into the

rubber latex to increase the stability of rubber latex because ammonia increased the negative surface charge of the rubber particle.

Kawahara *et al.* (2004) studied the effect of urea treated DPNR for removal of the protein from natural rubber latex and investigated the nitrogen content of latex by Kjeldahl method. The deproteinized natural rubber latex was prepared by incubation of the latex with 0.04 %wt of proteolytic enzyme and 1 %wt of SDS at 32 °C for 12 h. Then, the deproteinized natural rubber was incubated with 0.1 %wt urea and 1 %wt SDS at 30 °C for an hour followed by centrifuged twice. The nitrogen content of NR, urea-treat natural rubber, DPNR, and urea-treat DPNR were 0.380, 0.020, 0.017, and 0.008, respectively. From the result, urea was effective in the removing of the protein from the rubber. The urea-treat method did not cleavage any chemical linkage but it attached just on the surface of rubber particle through physical interaction.

Tarachiwin *et al.* (2005) studied the reducing of protein in DPNR by treating with lipase and phosphatase as enzymes and then analyzed the chain-end group (α-terminal). After the treatments of enzyme, the molecular weight and the content of long chain fatty acid ester group of DPNR were decreased from about 6 to 2 per rubber molecule. The decreases of ester content and molecular weight of DPNR were caused by the decomposition of branch-point. The NMR spectrum was used to measure the rubber chain-end which was represented by the acylglyceride and phospholipid groups. Hence, the presence of this groups was confirmed the success of treating DPNR with the enzymes.

Maznah *et al.* (2008) studied the effect of soaking pre-vulcanized NRL film in a KOH solution at various pH values (9-14) on the crosslinking density, mechanical properties, and extractable protein content (EP). Pre-vulcanized NRL films were soaked in the KOH solution and then dried at room temperature before testing. The crosslinking density of rubber film was evaluated by using the Flory-Huggins equation. After soaking the pre-vulcanized NRL film in the KOH solution, EP was decreased with increasing pH value until pH reached 10 because the protein molecule was hydrolyzed and then broken down. Hence, the small pieces of broken protein were easily removed by washing with water. Moreover, removing protein decreased the crosslinking density of film as the protein acted as a crosslinker. The

mechanical properties of soaking rubber film were reduced with increasing the pH of KOH solution due to the decreasing crosslinking density of rubber film.

Nawamawat *et al.* (2010) studied three different DPNR methods to reduce the protein content inside rubber latex. The three different methods were the enzymatic treatment, washing surfactant, and saponification methods. The enzymatic treatment used 0.04 % (w/v) of proteolytic enzyme in 1 % (v/v) of Tritan® X-100 by incubation at 37 °C for 24 h. For the surfactant washing method, fresh field latex was diluted to 15 % (v/v) of dry rubber and then added with 0.1 % (w/v) of SDS followed by centrifugation at 19,000 rpm for 60 min and then the procedure wasd repeated for 3 times. For the saponification method, the diluted fresh field rubber (15 % v/v of dry rubber) was added with 0.5 % (v/v) of Tritan® X-100 and 2 % (w/v) of NaOH at 70 °C. The nitrogen content of the samples was analyzed by a LECO-FP258 Nitrogen Analyzer. The nitrogen content of fresh field latex, enzymatic treatment, surfactant washing, and saponification method were 0.65, 0.14, 0.02, and 0.12 %wt, respectively. The best result of DPNR was shown in the surfactant washing method and the enzymatic treatment and saponification method showed the same efficiency.

Amnuaypornsri *et al.* (2010) studied the purification of fresh natural rubber latex (FL) by using the enzymatic treatment and saponification method with and without soaking process which affected the process efficiency. The deproteinized rubber with enzymatic treatment (DPNR) was used with 0.04 % (w/v) of proteolytic enzyme with 0.5 % (w/v) SDS and incubated at 37 °C for 12 h. Saponified natural rubber (SAP-NR) was prepared by using FL with 1.5 % (w/v) NaOH and 0.2 % (w/v) Tritan® X-100 at 70 °C for 3 h. The soaking process (SAP/SK-NR) was prepared by soaking SAP-NR in a 2 % (w/v) aqueous NaOH solution for 24 h. The nitrogen content was analyzed by a Leco Nitrogen Analyzer (model FP 528). The nitrogen content of FL, DPNR, SAP-NR, and SAP/SK-NR were 0.364, 0.109, 0.110, and 0.094 %wt, respectively. The residual protein in the rubber was confirmed by the nitrogen content. The process efficiency was reported which was analyzed by the Mooney viscosity. The viscosity of SAP-NR showed the lowest value. Thus, the processability of FL could be improved by the saponification method.

Kawahara and Chaikumpollert (2012) studied the rubber nano-matrix structure by the graft-copolymerization of styrene onto DPNR. The DPNR was prepared by a proteolytic enzyme (E-DPNR) and a urea treatment (U-DPNR) to reduce the protein content in the rubber. The nitrogen content of rubbers was measured by the Kjeldahl method. Styrene and acrylonitrile monomer were used as monomers for grafting on the DPNR backbone by using tert-butyl hydroperoxide with tetraethylene pentamine as an initiator. The nitrogen content of pure natural rubber, E-DPNR, and U-DPNR were 0.38, 0.017, and 0.020 %wt, respectively. With increasing urea incubation temperature of U-DPNR from 30 to 60 °C, the nitrogen content of U-DPNR increased to about 0.025 %wt (from 0.020 %wt). In case of E-DPNR, the protein was not cleaved with any chemical linkage. The enzyme were attached just onto the surface of rubber particle through physical interaction. The grafting of styrene on the DPNR showed the highest conversion and grafting efficiency at styrene feed of 1.5 mol/kg-rubber in E-DPNR. The grafting efficiency depended on the feed of styrene where the maximum efficiency was obtained at 1.5 mol/kg-rubber.

Kanjanathaworn *et al.* (2013) studied the effect of surphur prevulcanized natural rubber (SPNR) coated by poly (methyl methacrylate) nanoparticle (PMMA) for reducing the toxicity of SPNR. PMMA was synthesized via radical polymerization by mixing 2g of methyl methacrylate monomer (MMA), 0.01-0.08 g of 2,2`-Azobisisobutyronitrile (AIBN), and 0.25 g of hexadecane in a chitosan solution and then stirred for an hour. The PMMA was in the particle form with an average size of 380 nm. The SPNR was immersed in the PMMA solution. The surface roughness of SPNR increased when immersing SPNR into PMMA solution. Thus, this result confirmed that PMMA was coated on the SPNR surface. The L-929 fibroblast was used as the cell model for cytotoxicity testing. The PMMA coated SPNR could reduce the toxicity because PMMA on the SPNR surface reduced of direct contact between latex proteins and human skin.

Lee *et al.* (2014) studied the toxicity of orthodontic latex rubber bands which used in the oral cavity. The cytotoxicity test of rubber bands was investigated by using the extract of rubber band with mouse fibroblasts cell (L929) and human gingival fibroblast cell (HGFs). The NR bands were stretched to three times (3L) of

initial length and the original length (L) was used for cytotoxicity testing. The nitrogen content of rubber bands was about 1.60 %wt. as measured by a 2400 Series II CHNS/O element analyzer (Perkin Elmer, USA). The extracts of rubber band (L and 3L) were diluted from 100% extract to 50, 25, 12.5, and 6.25% extracts for the cytotoxicity tests of L929 and HGFs. The cytotoxicity testing of L929 and HGFs passed at 6.25 and 12.5% of diluted extract solution. Hence, the remaining of nitrogen content which passed the cytotoxicity test at 6.25 and 12.5 were 0.1% in L929 and 0.2% in HGFs.

DPNR was used for TDD application. Suksaeree *et al.* (2012) prepared the nicotine transdermal patches (NTPs) by blending DPNR with hydroxypropylmethyl cellulose (HPMC) and DBP as a matrix membrane for nicotine (NCT) delivery. The concentration of NCT in the NTPs was 2.5 mg/cm^2. The release of NCT used the diffusion area of NTPs of 1.77 cm^2 and a PBS buffer with a pH of 7.4 at 37 °C was used as the buffer solution. The release of NCT was studied along with the permeation through pig skin. In the result of NCT release, the effect of backing layer type showed the higher release of NCT than without backing layer because the backing layer protected the undesirable evaporation of NCT to the outer surface of the patch. The morphology of film after NCT released showed the various numbers of pores and cavities. The releasing of NCT through the pig skin showed a lower NCT permeation when compared with Nicotine ll TTS-20, a commercial NTP, without the backing layer because of no enhancer effect from DNRL/HPMC/DBP blending preparation. The increase of moisture vapor transmission rate increased the NCT permeation because of the increasing hydration at the skin. The highest skin permeation occurred at the lowest oxygen transmission because of the highest occlusive phenomena.

Pichayakorn *et al.* (2013) studied the nicotine release from a reservoir-type natural rubber patch by controlling layer prepared from deproteinized natural rubber latex (DNRL). The nicotine transdermal patch (NTPs) was consisted of a concentrated nicotine solution between a backing layer and a controlling layer which was then constructed by a heat-sealing technique. A Franz diffusion cell was used to study the nicotine permeation by using pig skin as a membrane. The thickness of controlling layers were at 100, 200, and 300 μm. The permeation rate was increased

by decreasing the thickness of controlling layer. Then, amount of nicotine solution was varied at 1.75, 2.50, and 4.25 mg/cm^2. The percentage of nicotine permeation and permeation rate were increased when increasing the amount of nicotine solution in the reservoir due to the increasing of nicotine concentration gradient.

2.4 UV Curing

Crosslinking a polymer is the method to produce highly crosslinked networks with high thermal stability, mechanical strength, and resistance to solvent absorption through chemical crosslink or radiation crosslink. The radiation crosslink is wildly used in several applications. For example, Rosli *et al.* (2003) studied epoxidized palm oil (EPO) that was cured with ultraviolet (UV) radiation by using their radical, cationic, or hybrid initiation. In this study, a cationic curing system was used. Triaryl sulphonium hexafluorophosphate (UVI 6990) and triaryl sulphonium hexafluoroantimonate (UVI 6974) were used as cationic photo initiators. The samples were cured using a 20 cm-wide IST UV machine under a condition of current 7.5A and 4 m/min conveyor speed. The cured rate and mechanical properties of cured films depended on the epoxy content in EPO. The gel content and shorter cured time were obtained with increasing oxirane oxygen concentration. Increasing the amount of EPO, the pendulum hardness decreased because of the increase in the fatty acid content that depended on the internal plasticizing effect. EPO could dissolve antimony salt easier than phosphate salt because the phosphate salt was of a bigger anion size, so antimony salt had a higher curing rate.

Do *et al.* (2008) studied the effect of a mono-functional hydrogenated rosin epoxy methacrylate (HREM) as synthesized from hydrogenated rosin and glycidyl methacrylate, with tetramethylammonium bromide as an initiator. A UV-crosslinkable polyacrylates was used as a pressure sensitive adhesive (PSA) by UV-crosslink system at various levels of UV-crosslinkable acrylic PSA and doses of UV. This work showed that hydrogenated rosin and HREM were miscible with acrylic PSAs at molecular level. FTIR data showed the concentration of benzophenone groups in the PSAs at 1580 cm^{-1} so the ability of crosslink depended on the

concentration of bezophenone and UV doses. However, the crosslink ability decreased in the system that had a higher amount of hydrogenated rosin.

Matsukuma *et al.* (2009) studied the molecular design and prepared and characterized a stimuli-responsive ultra-thin hydrogel film by photo-crosslinking. The photoreactive 4-aminobenzophenone (BP) was grafted onto the side group of poly(N-isopropylaclylamide-co-2-carboxyisopropylaclylamide)[poly(NIPAAm-co-CIPAAm)] to obtain a photo-crosslinkable polymer [poly(NIPAAm-co-CIPAAm)-BP] by a condensation method. The crosslinking reaction by UV-irradiation used an ultra-high-pressure Hg lamp. The photo-crosslinkable polymer was investigated by a quartz crystal microbalance (QCM). The QCM frequency shifted because of the poly(NIPAAm-co-CIPAAm)-BP adsorption but did not differ after coating one or twice because the adsorption was at equilibrium after five repeated spin-coatings. As polymer concentration increased so the QCM frequency shift also increased. However, the roughness of hydrogel film did not change before and after the UV-curing.

Xue *et al.* (2013) studied the UV-curing to prepare silicon rubber (SRs) by thiol-ene click chemistry. The properties of SRs depended on the amount of methylvinyl siloxane as polymer and poly(mercaptopropylmethylsiloxane) as a crosslinker. The system used 2,2-dimethoxy-2-phenylacetophenone(DMPA) as a photoinitiator. The tensile testing showed that the content of methylvinyl siloxane affected the mechanical properties of SRs. The content of methylvinyl siloxane was 0.3%mol, the mechanical properties of SRs would be close to those of the thermal radical curing. The DMA data showed that the α-transition peak decreased with increasing vinyl content because the peak height could be related to the crosslink density in an amorphous polymer. From the DMA result, SRs at high vinyl content showed high uniformity of thiol-ene network. SRs had high thermal stability using UV-curing.

Lee *et al.* (2013) studied the effect of photo-initiator content and UV doses in a UV-curing system. UV-curing system was used to produce a semi-interpenetrated structured polymer network of urethane epoxy adhesives in wafer using a hexafunctionacrylate monomer. Hydroxy dimethyl acetophenone was used as a photo-initiator. Methyltetrahydrophthalic anhydride and triphenylphosphine were

used as curing agents. The first step was the synthesis of silicon urethane methacrylate using polydimethylsiloxane and isophorone diisocyanate, and then 2-hydroxymethylmethacrylate was added. The second step was the preparation of dual-curable adhesive by blending diglycidyl ether of bisphenol A, dipentaerythritol hexacrylate, and a photo-initiator. The result showed that the amount of photo-initiator did not only affect the UV curing behavior, but thermal stability was affected in the UV-curing system depending on the UV-initiator content.

UV curing was developed to be used with the rubber. Phiyocheep and Duangthong (2000) studied la iquid natural rubber (LNR) as cured by ultraviolet (UV) by fixation of photosensitive molecule of LNR. Irgacure 184 and Darocur 1173 were used as photo initiators. LNR was treaded with in situ performic acid to obtain epoxidized liquid natural rubber (ELNR) and then photosensitive acrylic acid was added. The epoxide ring opening reaction of ELNR was reacted at 80 °C, faster than the reaction at 60 °C. The UV curing system used light from a 200 W medium pressure Xenon Mercury lamp with the radiation of 314 nm wavelength. The reaction at temperature of 80 °C was faster than the reaction at 60 °C because of increasing of probability of molecule collision. In this system, with and without photo initiator, it showed no significant exotherm detected after 30 min of UV applied because the reactivity of the acrylated rubber under UV irradiation was poor. This was because the long pendent isoprenic chain lengths limited the overlap of their function.

Choi *et al.* (2005) produced the crosslinked-electrospun of butadiene rubber (BR) via in situ UV-curing system at room temperature. The electrospinning was used to produce the butadiene rubber where tetrahydrofuran was used as a solvent. The experiment used a UV lamp for curing the butadiene fiber at the bottom of the collector to avoid the UV light to shine against the polymer solution. In the polymer solution, 2-methyl-4-(methylthio)-2-morpholinopropiophenone and trimethylol-propane 3-mercaptopropionate were used as the photo-initiator and crosslinking agent, respectively. The results showed that the diameter of cured-electrospun fiber was 1-4 μm and was of a circular shape. The glass transition temperature increased when increasing crosslinking agent because the molecular movement of BR was more restricted, and thus more energy was required for the polymer chains to move.

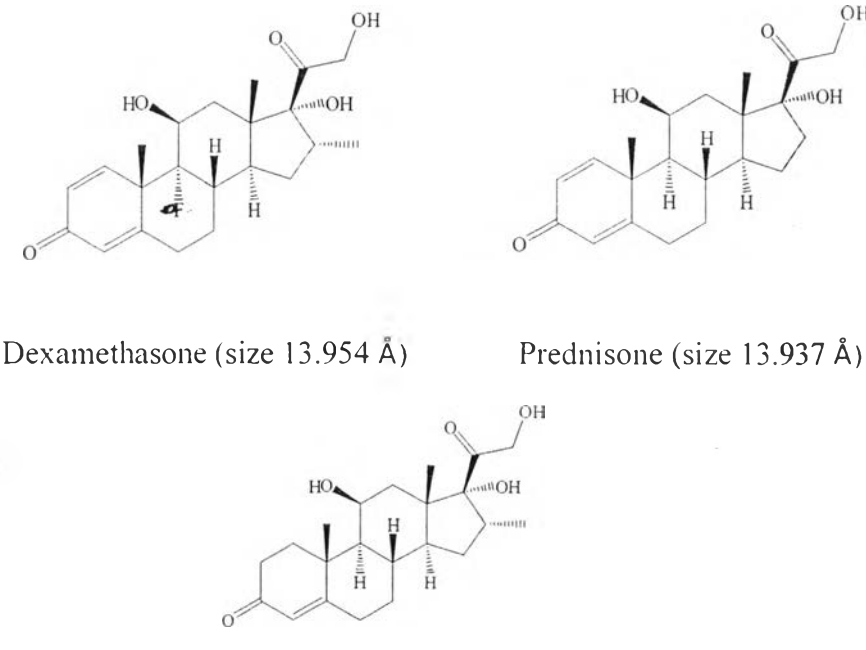
The mechanical properties of the electrospun were increased by increasing photo-initiator content because they were governed by both the slippage of crossing fibers and the breaking of fibers of permanently bonded junctions between netting fibers.

2.5 Anti-inflammatory Drugs

Anti-inflammatory drugs are usually used to reduce an inflammation as well as other medical conditions that come with it. The main types of anti-inflammatory drugs are glucocorticoids, non-steroidal anti-inflammatory drugs, immune selective anti-inflammatory derivatives, and herbs.

2.5.1 Glucocorticoids

Steroids or glucocorticoids can decrease the inflammation by reacting with intracellular receptors, and glucocorticoids receptors, which are uniquely shaped (Bhondwe, 2011).



Dexamethasone (size 13.954 Å) Prednisone (size 13.937 Å)

Hydrocortisone (size 13.948 Å)

Figure 2.4 The structure of some glucocorticoids.

2.5.2 Non-steroidal Anti-inflammatory Drugs, NSAIDs

NSAIDs can reduce inflammation by neutralizing cyclooxygenase (COX) enzymes, which promote the synthesis of inflammation substances. There are many regularly NSAIDs, for example, aspirin, diclofenac, ibuprofen, and indomethacin (Bhondwe, 2011).

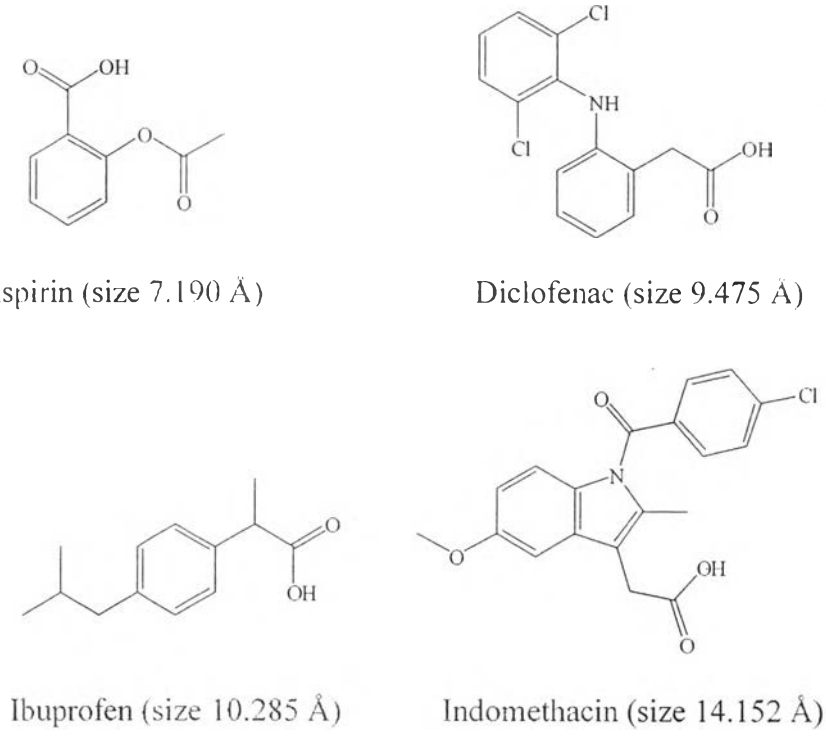


Figure 2.5 The structure of common NSAIDs.

2.5.3 Immune Selective Anti-inflammatory Derivatives, ImSAIDs

ImSAIDs are a class of peptides which are relatively new in medicine. Examples of these peptides are sub-mandibular gland peptide-T (SGP-T), and phenylalanine-glutamate-glycine peptide (FEG). They respond to the inflammation in a different way from glucocorticoids and NSAIDs. ImSAIDs modify the activation of white blood cells in a way that prevents the release of chemicals that generate and increase the inflammatory process.

2.5.4 Herbs

Several herbal extracts are used to reduce inflammation. An extract from willow-bark is the most well-known, acetylsalicylic acid (aspirin).