CHAPTER 2

LITERATURE REVIEWS

2.1 Arthritis

Arthritis is a chronic inflammatory disease resulting from inflammation of the joints or breakdown of cartilage in the joints. It affects people of all ages particularly in adult. There are over hundred kinds of the arthritis especially rheumatoid arthritis and osteoarthritis which are the major inflammatory diseases affecting people worldwide [1].

Common symptoms of the arthritis include pain, stiffness and swelling in or around the joints. Therefore, the treatment of arthritis diseases depends on the stage or type of arthritis. Treatment for early stage can be treated with corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), including naproxen, diclofenac, ketoprofen, ibuprofen and celecoxib. All these drugs which suppress swelling and pain possess several adverse effects. The people who used long term corticosteroids for the management of rheumatoid arthritis have suffered from some serious adverse effects, such as hypertension, hyperglycemia, muscular weakness, increased susceptibility to infection, osteoporosis, glaucoma, psychiatric disturbances, growth arrest, etc. Similarity, patients who take NSAIDs for a long time may cause serious side effects such as stomach irritation, bleeding ulcers or kidney disfunction [2].

Rheumatoid arthritis is the most common type of arthritis. It is a chronic inflammatory condition involved in up-regulation of pro-inflammatory cytokines and matrix metalloproteinases (MMPs), resulting in joint inflammation and erosion. It affects 0.3–1.0% of the general population and is more prevalent among women in developed countries. Rheumatoid arthritis is an autoimmune disease in which the immune system attacks mostly joints. The immune cells called lymphocytes are activated and chemical messengers (cytokines, such as tumor necrosis factor [TNFα] and interleukin-1 β [IL-1β]) are expressed in the inflamed areas. Signs of the symptom include swollen joint, stiffness often in the morning, warmth and redness around the joints [1].

Osteoarthritis is a common degenerative condition of the joints associated with aging, leading to pain, stiffness, and reduced mobility affecting joints. It affects 9.6% of men and 18% of women aged more than 60 years. Osteoarthritis usually happens gradually over time. Some risk factors that might lead to it include overweight, getting older, joint injury, genetic defect in joint cartilage and stresses on the joints from certain jobs or playing sports [7].

2.2 Alternative herbs for arthritis

There are many herbal remedies that can help to ease arthritis pain. The following are a few popular herbs in Thailand which help to anti-inflammatory relief for arthritis patients and in individuals recovering from other muscle, tendon, and joint inflammatory conditions. These agents may not only prevent structural damage of arthritis joints caused by tissue and bone breakdown, but also be safe, inexpensive, highly tolerated and convenient for many patients.

2.2.1 Plantain

Figure 2.1 *Plantago major* Linn.

(http://www.prota4u.org/search.asp)

Plantain (*Plantago major* Linn.) belonging to the family Plantaginaceae is a perennial herb found wild throughout the whole of Europe and temperate Asia. Every part of the plant has been used in many traditional medicines. Particularly, leaves and seeds of *P. major* have been used for centuries to treat diseases relating to skin, digestive organs and blood circulation like wounds, inflammation and hypertension. The extract from *P. major* leaves contain high content of phenols, flavonoids and tannins that involved in bioactive effect especially on wound healing, and to have antiulcerogenic, anti-inflammatory, antioxidant, anticarcinogenic and antiviral activities [8].

2.2.2 Plai

Figure 2.2 *Zingiber cassumunar* Roxb.

(http://www.eldercarethailand.com/content/view/519/54/)

Zingiber cassumunar Roxb. commonly known in Thailand as plai, is used in folk medicine for the treatment of conditions such as inflammation, sprains and strains, rheumatism, muscular pain, wounds as well as activity as a smooth-muscle relaxant. The active compound of *Z. cassumunar* extract, (E)-4-(3',4'-dimethoxyphenyl) but-3-en-1-ol (compound D), can effect as prostaglandin inhibitor which suppressing cytokine-induced catabolic genes (MMP-1, -2, -3, and -13) which caused cartilage erosion in rheumatoid arthritis. It was indicated that *Z. cassumunar* has long been used to reduce joint pain and inflammation [9].

2.2.3 Turmeric

Figure 2.3 *Curcuma longa* Linn.

(http://www.aopdh06.doae.go.th/herbs/Curcuma%20longa%20Linn.html)

Turmeric (*Curcuma longa* Linn.) derived from the rhizomes of the plant and widely use in medicine as a treatment for inflammatory conditions. *C. longa* is a perennial member of the Zingiberaceae family and is cultivated in India and other parts of Southeast Asia. The primary active constituent of turmeric is curcumin, a yellow pigment which powerful anti-inflammatory agent. It has been shown to be as effective as the drug phenylbutazone in reducing pain swelling and stiffness in rheumatoid arthritis patients. Comparing curcumin to NSAIDs (non-steroidal anti-inflammatory drugs), curcumin was found to be more potent than aspirin, ibuprofen, naproxen, and several others. Daily administration of purified curcumin (4 mg total curcuminoids/kg/d) inhibited joint inflammation in both the acute and chronic phases of arthritis. Therefore, curcumin has potent anti-inflammatory activity similar to the action of steroids, but without the side effects [10].

2.2.4 Ginger

Figure 2.4 *Zingiber officinale* Roscoe.

(http://www.upcorner.com/baby1_ginger.html)

Ginger (*Zingiber officinale* Roscoe.) belongs to Zingiberaceae family. The useful part of ginger is rhizome. Ginger extract is one of the effective arthritis joint pain remedies recommended by physicians. The major active compounds are called gingerols which found in ginger's oleo-resin. These compounds are responsible for anti-inflammatory, relieve pain, and decrease joint swelling in arthritic patients. The mechanism of the anti-inflammatory activity could be due to the inhibition of cyclooxygenase and lipooxygenase pathways by certain ginger constituents. Specifically, they are 6-gingerol, 10-dihydrogingerdione, and 10-gingerdione. Since ginger has anti-inflammatory properties, ginger oil is widely used to massage on sore or aching muscles offering pain relief. In a pilot study, six patients with rheumatoid arthritis consumed 5 g of fresh ginger or 0.5-1.0 g of powdered ginger per day. After three months, every patient reported a reduction in pain, better joint mobility, and less swelling and morning stiffness [11].

2.3 Longan

Longan (*Dimocarpus longan* Lour.) is an evergreen tree of the Sapindaceae family. Longan is a subtropical fruit, which is widely grown in China and South East Asia, including Thailand, Vietnam, and Philippines. As it is a highly attractive fruit that revealed various medical effects, so it possesses high commercial and pharmaceutical value [12].

Figure 2.5 *Dimocarpus longan* Lour.

(http://it.doa.go.th/vichakan/news.php?newsid=4)

In addition, longan seed have been found to be a rich source of antioxidant phenolic compounds such as gallic acid, corilagin and ellagic acid and has shown strong free radical-scavenging activity. Especially, the contained gallic acid and ellagic acid are known to have anti-inflammatory effect. The previous study of Prima Herb (Thailand) Co., Ltd. has investigated chondroprotective effect of longan seed extract, containing highly gallic acid, on cartilage degradation induced by the most important cytokine (IL-1-β) which causes degenerative joint diseases, using Cartilage Explant Model. The results revealed that the extract at least 10 μg/ml could inhibit the matrix metalloproteinase enzymes (pro-MMP-2 and pro-MMP-9 induced MMP-2 and MMP-9, respectively) in human synovial cells. The activities of MMP-2 and

MMP-9 involve in cartilage degradation of degenerative joint diseases. Moreover, the extract had significantly suppressive effect on pro-inflammatory agent (IL-1-β) activity. It may possible to propose that the longan seed extract has chondroprotective activity which simulated the pathology of degenerative joint diseases [4].

2.3.1 Major phenolic compounds from longan seed extract and their anti-inflammatory activities

The major phenolic compounds from longan seed extract as gallic acid, ellagic acid and corilagin involved on anti-inflammatory activity. There are presented as following:

Gallic acid [13]

Molecular formula: $C_7H_6O_5$

Molar mass: 170.12 g/mol

Solubility: water, ethanol

Chemical structure:

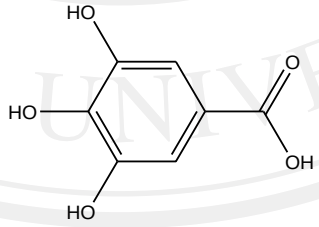


Figure 2.6 Gallic acid

Gallic acid (3,4,5 -trihydroxybenzoic acid) is a natural polyphenol from gallnut and green tea. Gallic acid has been reported to show anti-oxidant, anti-inflammation, anti-microbial and radical scavenging activities. It has been able to show inhibit immunoglobulin E (IgE)-induced histamine release from mast cell.

Additionally, 10 μM of gallic acid has been also able to decrease pro-inflammatory cytokine gene expression and production of TNF-α and IL-6 in human mast cells [14].

Ellagic acid [13]

Molecular formula: $C_{14}H_6O_8$

Molar mass: 302.197 g/mol

Solubility: water, alkalines, pyridine, alcohol

Chemical structure:

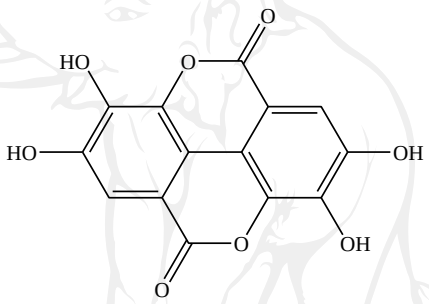


Figure 2.7 Ellagic acid

Ellagic acid is a polyphenolic compound that found in various fruits and vegetables. Recently, it found to show possible involvement in the inflammatory cascade through inhibition of cyclooxygenase (COX) protein expression, as well as anti-inflammatory effects in the animal model. Moreover, there is a study on the anti-inflammatory effects of ellagic acid compared with COX inhibitors in male Sprague-Dawley rats. It was revealed that ketorolac (COX inhibitor) was significantly reduced paw edema at 4 hours whereas ellagic acid was significantly reduce paw edema at 8 hours. At 24 hours, only ellagic acid was effective. Therefore, ellagic acid may be effective against inflammation along with prolonged onset and duration of action [15].

Corilagin [16]

Molecular formula: $C_{27}H_{22}O_{18}$

Molar mass: 634.46 g/mol

Solubility: DMSO, methanol

Chemical structure:

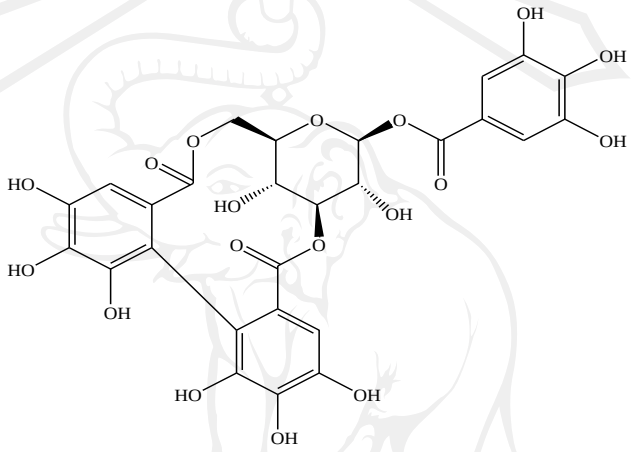


Figure 2.8 Corilagin

Corilagin (beta-1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-Dglucose) is a novel member of the tannin family which has been discovered in many medicinal plants. It has been confirmed in many pharmacological activities particularly anti-inflammatory activity. Corilagin can reduce production of pro-inflammatory cytokines and mediators TNF-α, IL-1β, IL-6, NO (iNOS) and COX-2 on both protein and gene level by blocking NF-κB nuclear translocation. Therefore, the anti-inflammatory effect of corilagin is attributed to the suppression of pro-inflammatory cytokines and mediators by blocking NF-κB activation. Moreover, it promoted the regression of inflammation and has a good prospect to be used in many inflammation related diseases [16].

2.4 Transdermal patch

Transdermal delivery systems (TDSs) also known as transdermal patch is dosage forms involving the control of active compounds transport to skin epidermal and/ or dermal tissues for local or systemic therapeutic effect and suited for the treatment of chronic disorder [18].

2.4.1 Types of transdermal patches

Although transdermal systems are classified in different types, transdermal patches can be divided into three main categories depending on the incorporation style of the drug in the system as following [18-19]:

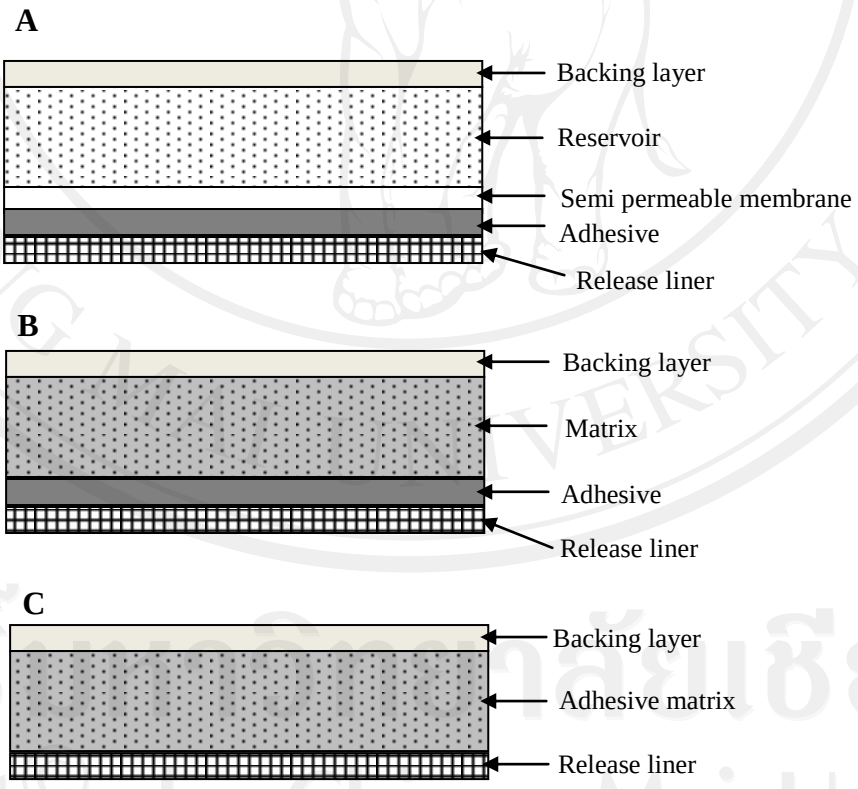


Figure 2.9 Schematic representation of transdermal patch types: A. Reservoir, B. Matrix, C. Drug-in-Adhesive transdermal systems.

A) Reservoir Systems: In these systems, the drug is in a reservoir as liquid. Drug molecules are contained in the storage part, as a suspension in a viscous liquid or dissolved in a solvent. The membrane made of a polymer with different structure, which separates the reservoir from the adhesive layer. It was used for controlling the release rate of the drug. The adhesive polymer on the exterior surface of the membrane enables the transdermal to adhere to skin. In these systems, drug release rate can be controlled by membrane thickness and adhesive layer .

B) Matrix Systems: In this type of systems, the drug is dispersed homogeneously within a polymer matrix which has hydrophilic or lipophilic polymer. The patch is adhered on the skin with an adhesive polymer that is sensitive to direct pressure and then covering this system with an impermeable backing layer. Since there is no controlling membrane, the release of the drug is related to the surface area to which the patch is applied or the permeability of the skin.

C) Adhesive Systems: In these systems, the drug reservoir is formed by dispersing the drug in an adhesive polymer. Under the drug reservoir layer, there exists an adhesive membrane controlling the drug release rate. These systems are particularly appreciated by patients, because they are thin, flexible, comfortable and conformable.

2.4.2 Basic composition of transdermal patches

Although transdermal systems can be design as different type systems mentioned above, the basic components which generally are used in the formulations of almost all type of transdermal patches [20].

2.4.2.1 Polymer

Polymers are the backbone of transdermal patches, which control the release of drug from the device. Different classes of polymeric materials have been used to control the release rate of the drug. The mechanism of drug release depends on the physicochemical properties of the drug and polymer which used in the formulation. The following criteria should be satisfied for a polymer to be used in a transdermal system [21].

- Molecular weight, glass transition temperature, chemical functionality or polymer must allow diffusion and release of the specific drug.
- The polymer should permit the incorporation of a large amount of drug.
- The polymer should not react, physically or chemically with the drug.
- The polymer should be easily manufactured and fabricated into the desired product and in expensive.
- The polymer must be stable and must not decompose in the presence of drug and other excipients used in the formulation, at high humidity conditions, or at body temperature.
- Polymers and its degradation products must be non toxic.

Possible useful polymers for transdermal patches are:

1) Natural polymers are obtained from nature (plants and animals) such as cellulose derivatives, zein, gelatine, shellac, waxes, gums, natural rubber, chitosan, pectin etc.

Chitosan is a cationic polymer composed of 2-amino-2-deoxy-D-glucosamine (D-glucosamine) linked β-D-(1-4) that obtained from deacetylation of chitin in alkali. The chemical structure is shown in **Figure 2.10**. The most easily exploited sources of chitin are the protective shells of crabs, shrimp and squid pen. Chitosan is readily soluble in organic acidic solution but low solubility at pH of 7.4 or higher pH. The viscosity of chitosan solution is affected by molecular weight, ionic strength, pH and temperature of solution. High molecular weight chitosan polymers provide a higher solution viscosity than low molecular chitosan oligomers. Moreover, the viscosity of chitosan solution increases with an increase in chitosan concentration and degree of deacetylation but decrease in solution temperature and pH. However, under a similar pH environment, the solution viscosity chitosan differs with using difference in organic acids [22].

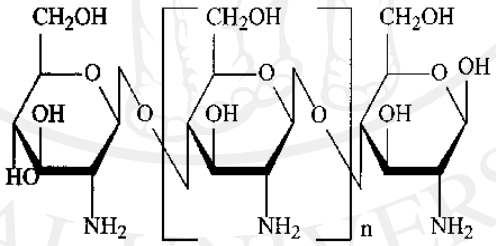


Figure 2.10 The representative structure of chitosan

Chitosan has shown to have a high ability to adhere the skin due to ionic interaction between positively charged in chitosan and negatively charged of the skin. Chitosan is a biodegradable and biocompatible polymer. It has low level of toxicity and lack of irritant and allergic effects. As such, it is widely used in a variety of pharmaceutical, medical and industrial applications. Owing to its adhesive,

absorption enhancing and sustained-release characteristics, chitosan has been employed as excipient in various dosage forms delivered [23].

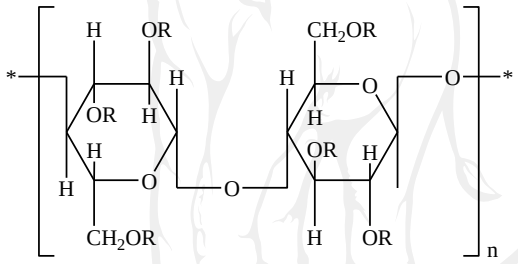
Pectins are mixture of polysaccharides, in which the polymer backbone mainly comprises α-(1-4) D galacturonic acid residues. Pectins obtained from citrus peel or apple pomades, both of which are by-products of juice manufacturing process. Apple pomade contains 10–15% of pectin on a dry matter basis while citrus peel contains of 20–30% [24]. Pectins are soluble in water and formed gel for a wide range of pharmaceutical applications such as film coating of colon-specific drug delivery systems when mixed with ethyl cellulose, microparticulate delivery systems for ophthalmic preparations and matrix type transdermal patches. It has high potential as a hydrophilic polymeric material for controlled release matrix drug delivery systems, but its aqueous solubility contributes to the premature and fast release of the drug from these matrixes [25].

2) Semi-synthetic polymers are derived from naturally occurring polymers by chemical modifications such as hydroxyethyl cellulose, hydroxypropylmethylcellulose, etc [21].

Hydroxyethyl cellulose (HEC) occurs as a white, yellowish-white or grayish-white, odorless and tasteless, hydroscopic powder. It is nonionic, water soluble polymer which widely used in pharmaceutical formulations as thickening agent, binder, film and coating agent. The concentration of HEC used in formulation is dependent on the solvent and the molecular weight of the grade. HEC is insoluble in most organic solvents and good tolerance for dissolved electrolytes. Owing to the solution of HEC are relatively stable at pH 2-12 with unchanged of its

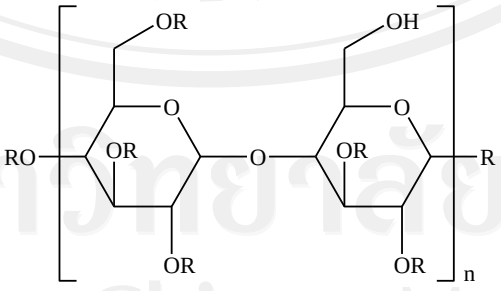
viscosity, it is widely used in cosmetic formulations and also be used in various delivery systems [26].

Hydroxypropylmethylcellulose (HPMC) is an odorless and tasteless, white or creamy white powder. It is widely used as a coating agent, film former, stabilizing agent, rate controlling polymer for sustained release and viscosity increasing agent. It is soluble in water forming a viscous colloidal solution but practically insoluble in chloroform, ethanol and ether. HPMC solutions are stable at pH 3-11 whereas incompatible with some oxidizing agent [26].



n = polymer degree, R = -H or -(-H_2-CH(CH_3)O-)-xH

Figure 2.11 The representative structure of HEC



R = H, CH_3 or -CH_2-CHOH-CH_3

Figure 2.12 The representative structure of HPMC

3) Synthetic polymers are manufactured in industry from chemicalsubstances through the polymerisation process such as polyvinyl alcohol, polyvinyl chloride, polyethylene, polyvinylpyrrolidone, etc

2.4.2.2 Drug [21]

The desirable properties of drug for transdermal patch should bechosen with great care as the following:

- The drug should have a molecular weight less than approximately 1,000 daltons.
- The drug should have affinity for both – lipophilic and hydrophilic phases.
- The drug should have low melting point.
- The drug should be potent, having short half life and be non irritating.

2.4.2.3 Penetration enhancers

The outermost layer of skin, the stratum corneum, has been considered a major transport barrier for transdermal diffusion. There are major categories for promoting the drug transport across the stratum corneum: physical and chemical enhancers [27]. Substances that promote the penetration of topically applied drug through the stratum corneum and epidermis are commonly referred to as penetration enhancers. The ideal properties for penetration enhancers acting within skin have been given as following [28]:

- They should be non-toxic, non-irritation and non-allergenic.
- They should be pharmacologically inert with no action at receptor sites within the body.

- They would ideally work rapidly, and the activity and duration effect should be both predictable and reproduction.
- They should be chemically and physically compatible with drugs and additives in the dosage form.
- Their effects should be completely and rapidly reversible upon removal of the material from the skin.
- They should be cosmetically acceptable with an appropriate skin “feel”.

To date, no material of penetration enhancer has been found all the ideal properties. There are several classes of penetration enhancers that have been used and examples of materials are provided in **Table 2.1**.

Table 2.1 Types and examples of penetration enhancers [29]

Chemical class	Examples
Fatty acid	Saturated fatty acid: stearic acid, valeric acid Unsaturated fatty acid: oleic acid, arachidonic acid
Alcohol	Aliphatic alkanols: ethanol-decanol Fatty alcohol: stearyl alcohol, lauryl alcohol
Amides	Urea, dimethylformamide, Azone®,
Fatty acid ester	Isopropyl myristate, ethyl acetate
Polyols	Propylene glycol, polyethylene glycol
Surfactants	Anionic: sodium lauryl sulfate Cationic: benzalkonium chloride, cethyltrimethyl ammonium bromide Nonionic: poloxamer, Brij®, Span® , Tween® Bile salts sodium cholate, sodium glycolate, lecithin
Sulfoxides	Dimethyl sulfoxide, decylmethylsulfoxide
Terpenes	Hydrocarbons: D-limonene, -pinene Alcohols: -terpineol, terpinen-4-ol Ketones: carvone, menthone Oxides: limonene oxide, 1,8-cineole Oils: anise oil, eucalyptus oil

Penetration enhancers have been found to increase transdermal drug transport via several different mechanisms that can be described as following [28]:

1) Act on the stratum corneum intracellular keratin, denature it or modify its conformation causing swelling and increase hydration.

2) Modify the intercellular lipid domains to reduce the barrier resistance of the bilayer lipids.

3) Alter the solvent nature of the stratum corneum to modify partitioning of the drug or of a cosolvent into the tissue.

2.4.2.4 Pressure sensitive adhesive (PSA)

PSA is a material that adheres with no more than applied finger pressure, is aggressively and permanently tacky, exerts a strong holding force, and should be removable from a smooth surface without leaving a residue. Because of the direct skin contact, PSA should be non-irritating, non-sensitizing, and to not cause systemic toxicity [30]. The most typically used PSA polymers are acrylates, polyisobutylenes and silicones.

Acrylates: are the most popular PSA which made by emulsion or solution polymerization of acrylic esters with acrylic acid and other monomers. There are several advantages of acrylates; good compatibility with wide ranges of drugs and additives, ease of processing and flexibility in improvement the polymer properties. They are hypoallergenic and the cost of manufacturing process is inexpensive comparing silicones. They also offer resistance to solvents, UV, light, elevated temperatures, plasticizers and sterilization methods. Moreover, they are highly resistant to oxidation. Therefore, stabilizer is not required when acrylates are chosen as a PSA in the formulation [31]. They are easily crosslinked, which can help improve their coadhesive properties where interaction between the drug, enhancers or solvents would degrade the adhesive.

Polymethacrylates (Eudragit®) are favorably used in transdermal drug delivery system because of their advantages as the above. These polymers have also been preferentially used to manufacture oral controlled release dosage forms. Recently, the use of Eudragit® acrylic as metrix polymers for transdermal systems has been extensively investigated [31].

Polymethacrylates are synthetic cationic acid and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid and methacrylic acid ester in varying ratios. Several different types of acrylates are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution [31]. Some chemical and trade names of polymethacrylates are shown in **Table 2.2**

Eudragit® NE 30 D is an aqueous dispersion of neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. It is extensively used in transdermal drug delivery system because of its sustained release properties and pH-independent drug release [30].

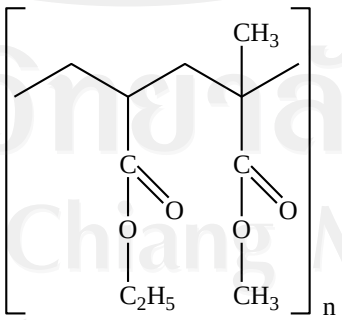


Figure 2.13 The representative structure of Eudragit® NE 30 D

Table 2.2 Chemical name and trade name of polymethacrylates [32]

Chemical name	Trade name
Poly (butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1:2:1	Eudragit E 100 Eudragit E 12.5
Poly (ethyl acrylate, methyl methacrylate) 2:1	Eudragit NE 30 D
Poly (methacrylic acid, methyl methacrylate) 1:1	Eudragit L 100 Eudragit L 12.5 Eudragit L 12.5 P
Poly (methacrylic acid, ethyl methacrylate) 1:1	Eudragit L 100-55 Eudragit L 30 D-55
Poly (methacrylic, methyl methacrylate) 1:2	Eudragit S 100 Eudragit S 12.5 Eudragit S 12.5 P
Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2	Eudragit RL 100 Eudragit RL PO Eudragit L 30 D Eudragit RL 12.5
Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1	Eudragit RS 100 Eudragit RS PO Eudragit RS 30 D Eudragit RS 12.2

Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is light yellow in color with the characteristic odor of the solvents. It is soluble in acidic buffer solutions (up to pH 5). Eudragit E is available as a 12.5% ready-to-use solution in propan-2-ol-acetone (60:40) [32].

Polyisobutylenes (PIBs): are used widely in transdermal drug delivery system because they can be modified easily for blending and compatible with many drugs. It is available in various molecular weights. In order to improve its adhesive properties, it needs to be blended with waxes, oils, solvents and other polymer as tackifiers, plasticizers and fillers. Because of its unsaturated characteristic, stabilizers are added to improve its chemical stability. This is main disadvantage in addition to tendency for allergic side effects [31].

Silicones: are expensive relative to other types of PSA. However, it is easier to modify their adhesive properties, including tack and cohesion. It is not required addition of antioxidants because of their natural chemical and thermal stability. Its major disadvantage is its unusually high price, which still prohibits its use in transdermal preparation [31].

2.4.2.5 Plasticizers

Plasticizers are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material**.** When addition of plasticizers, flexibilities of polymer macromolecules or macromolecular segments increase as a result of loosening of tightness of intermolecular forces [33-34].

By adding plasticizer to a polymeric material, elongation at break, toughness and flexibility are expected to increase, on the other hand tensile stress, hardness, electrostatic chargeability, Young's modulus and glass transition temperature are expected to decrease [35-36]. Many of the polymers used in pharmaceutical formulations are brittle and require the addition of a plasticizer into the formulation. Plasticizers are added to pharmaceutical polymers intending to ease the thermal

workability and modifying the drug release from polymeric systems. Additionally, they help to improve the mechanical properties by enhancing the resistance and tear strength of the polymer film [33].

The selection of plasticizers depends on the characteristics of polymer used to prepare transdermal formulation. The list of frequently used plasticizers in pharmaceutical formulations is shown in **Table 2.3**.

2.4.2.6 Backing membrane

The primary function of the backing membrane is to protect the system from external effects during administration. The materials should be impermeable for drugs and penetration enhancers. The backing membrane must be inert and not compatible with the drug and other substances used in the formulation. Moreover, it must have optimal elasticity, flexibility, and tensile strength [21].

2.4.2.7 Release liner

The release liner has to be removed before the application of transdermal system. It protects the formulation from external environment and also helps to prevent contamination. It should be easily peeled from the adhesive layer and should not damage the structure of adhesive layer [21].

Table 2.3 Plasticizers Used in the Pharmaceutical Formulations [37]

Group	Plasticizer	Hydrophilic/Lipophilic
Glycerol and esters	Glycerine, Glycerine triacetate, Glyceryltributyrate	Hydrophilic
Glycol derivatives	Propylene glycol, Poliethylene glycol	Hydrophilic
Oleic acid esters	Oleil oleate	Hydrophilic
Sugar alcohols	Sorbitol	Hydrophilic
Citric acid esters	Triethyl citrate, Tributhyl citrate	Hydrophilic
Phthalic acid esters	Dibutyl phthalate, Diethyl phthalate	Lipophilic
Sebacic acid esters	Dibutyl sebacate, Diethyl sebacate	Lipophilic
Tartaric acid esters	Diethyl tartarate	Lipophilic

2.4.3 Advantages of transdermal patch

Transdermal delivery systems (TDSs) also known as transdermal patch was emerged in order to increase the effectiveness of drugs or active substances via skin. TDSs are dosage forms involving the control of active compounds transport to skin epidermal and/ or dermal tissues for local or systemic therapeutic effect and suited for the treatment of chronic disorder. The main advantages that transdermal patch should posses are listed as following [17]:

- Control administration of a therapeutic dose at a desirable rate of delivery
- Maintenance of drug concentration within an optimal therapeutic range for prolong duration of treatment
- Self administration
- Reduction of side effects due to the optimization of the blood concentration time profile
- Minimization of the needs for frequent dose intent
- Enhancement of patient compliance