CHAPTER I

INTRODUCTION

The sun radiates energy in a wide range of wavelengths, parts of which are visible to human eyes. The shorter the wavelength, the more energetic the radiation, and the greater the potential for harm. The ultraviolet (UV) rays, which comprise the shortest of the nonionizing rays, are responsible for most of the photocutaneous changes. The UV radiation can be further divided into three categories; UVC, UVB, UVA (1) (Figure 1.1). The UVC (200-280 nm) although most energetic and most photoactive among the three, no UVC reaches the surface of the earth because of the absorption by ozone. In contrast, UVB (280-320 nm) and UVA (320-400 nm) can penetrate the ozone layer. The UVB radiation plays essential role in formation of vitamin D and increases skin pigmentation or tanning (2). In addition UVB inhibits or interferes DNA, RNA and protein synthesis, induces early and prolonged erythema responses that would lead to photoaging, skin cancer and immunosuppression (3-4). The UVB effects are direct in nature and do not require intermediate photosensitizer because nucleic acids, proteins and many biological molecules can directly absorb UVB radiation (5).

The UVA (320-400 nm) also produces a significant number of photobilogical effects. The UVA causes damages to the cells indirectly, the mechanism usually involves the induction of reactive oxygen species.[5-8] UVA rays induce both an immediate erythema, which diminishes within 2 hours and a delayed erythema response which reaches a peak in 12 to 24 hours (1).

In addition, penetration of UV radiation into skin varies with wavelength. It has been found that the UVA, which is less energetic than UVB, can penetrate deeper into the dermis, while UVB can penetrate only into the stratum corneum and the epidermis (Figure 1.2). At the same time, UVA contributes with UVB to photoaging and skin cancers.

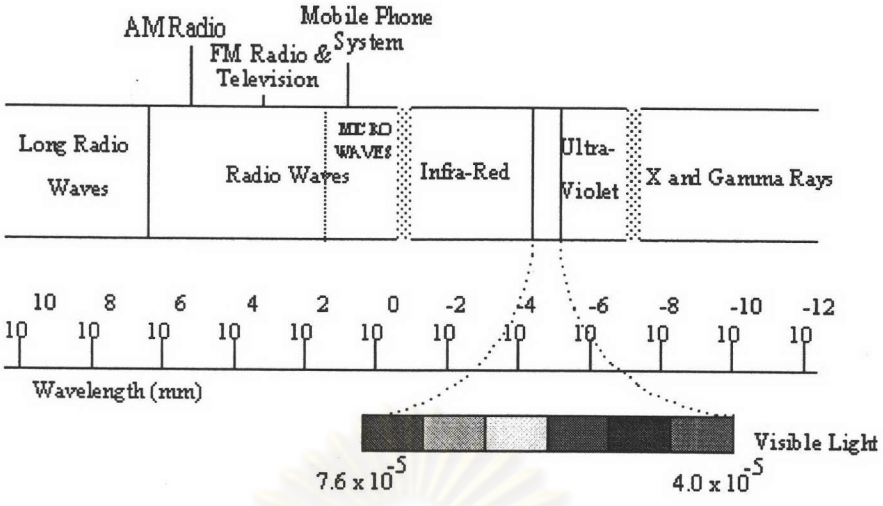


Figure 1.1 Electromagnetic spectrum.

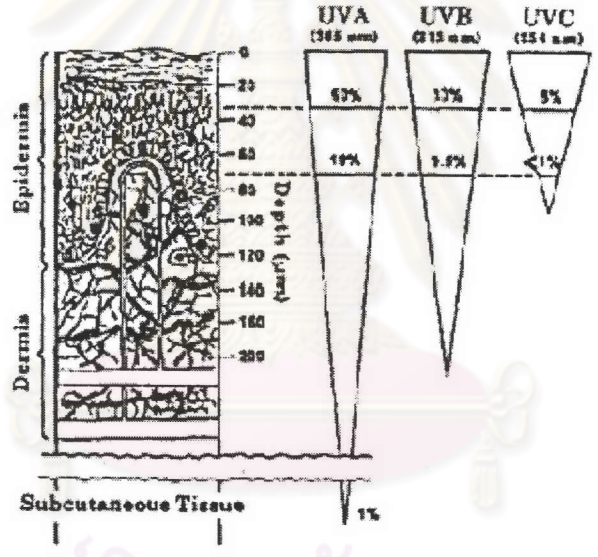


Figure 1.2 UV penetration into the skin.

Because of the expanding knowledge about the harmful effects of the solar UV rays on human skin, the use of sunscreen agents has become increasingly widespread.

1.1 Classification of Sunscreen Chemicals (1)

Sunscreen chemicals may be classified according to the type of protection they offer as either physical blockers or chemical absorbers.

1.1.1 Physical Blockers

A physical blocker is a chemical that reflects or scatters the ultraviolet radiation. Most of physical blocker are inorganic compounds. Its physical appearance is non-soluble and therefore, can reflect part of the UV radiation. Examples of physical blockers include zinc oxide, titanium dioxide and red petrolatum. Most physical blockers are currently being used in conjugation with organic UV filters to achieve high sun protection factors (SPF).

In addition to reflection and scattering, the UV filtering property of the physical blockers is also partly achieved because of their semiconductor properties. The energy gap between valence band and conducting band in titanium dioxide and zinc oxide correspond to wavelength of 387-405 nm and 384 nm, respectively. Therefore, photons of energy around that of the band gap between the valence band and the conduction band can be absorbed producing characteristic absorption band for the substances. Thus UV radiation is effectively scattered and absorbed by the particles, thereby making these substances suitable UV blockers. However, because of the semiconductor properties of these oxides, they have been increasingly used as photocatalysts for the degradation of organic pollutants in waste water (9). Since, by their nature, sunscreen preparations are exposed to sunlight, the photocatalytic behavior of these blockers needs to be considered. There are many reports which affirm that photoexcited titanium dioxide can cause cell death both *in vitro* and *in vivo* (10).

1.1.2 Organic Absorbers

These chemicals absorb the harmful ultraviolet radiation. They are soluble organic molecules whose absorption bands are in UV region. The choices of the correct compounds usually depend upon the following criteria (2):

Absorption Range Depending upon the desired UV absorption, a choice is made between one or more UVB filters, a certain bandwidth filter, or a filter corresponding to a combination of UVA and UVB filters.

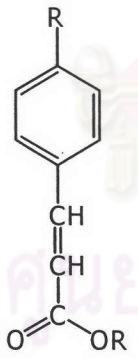
UVA absorber are chemicals that absorb radiation in the 320-360 nm region of the ultraviolet spectrum. Examples of UVA absorbers include benzophenone, anthranilates and dibenzoyl methane.

UVB absorber are chemicals having absorption band in the 290-320 nm region of the ultraviolet spectrum. Examples of UVB absorbers include *p*-aminobenzoate (PABA) derivatives, salicylates, cinnamates and camphor derivatives.

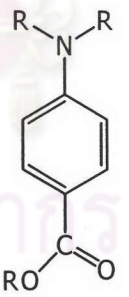
Solubility Whether a sunscreen is based on oil or aqueous gel, the chosen sunscreen compound must be compatible with its base. In the case of emulsion, sunscreen either water or oil soluble compounds can be used. Often a combination of water and oil soluble sunscreen is desirable due to cost or effectiveness considerations.

Sun Protection Factor (SPF) A ratio of the amount of UV radiation that produce erythema in skin covered by sunscreen to the amount of UVB radiation that produce a similar erythema in skin uncovered by sunscreen. The SPF value corresponds to the ability of sunscreen to protect against UV radiation.

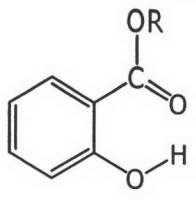
Examples of organic UV filters used in sunscreen industry are depicted in Figure 1.3



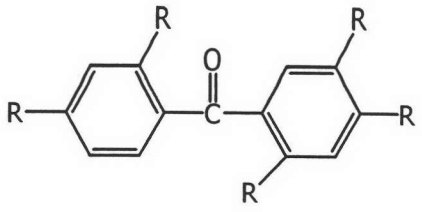
Cinnamate derivatives



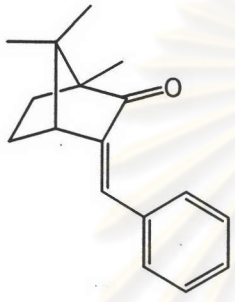
p-Aminobenzoate derivatives



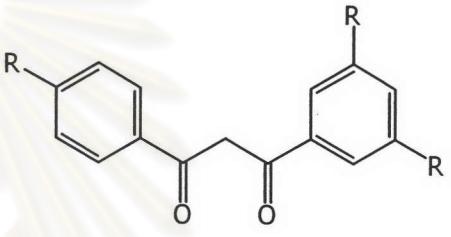
Salicylates



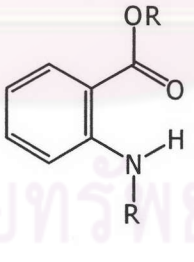
Benzophenone



Camphor Derivatives



Dibenzoylmethane



Antranilates

Figure 1.3 Groups of organic sunscreen filters currently used in sunscreen industry.

1.2 Mechanism of Sunscreen Action

In general chemical absorbers usually contain an aromatic ring conjugated with a carbonyl group. Often an electron-releasing group such as amine or methoxy group, is substituted in the *ortho-* or *para-* position of the aromatic ring. In addition, these molecules usually contain appropiated conjugated systems which make the energy gap between the ground state and the excited state fall to the UV region. The process of sunscreen action is called 'photophysical process', not a photochemical process and ideally no change in molecular structure should be observed. Mechanism of absorber molecule is depicted in Figure 1.4. The deactivation mechanism of organic filters is usually internal conversion and vibrational relaxation. However, red shifted fluorescence deactivation mechanism can also be detected in some systems (11).

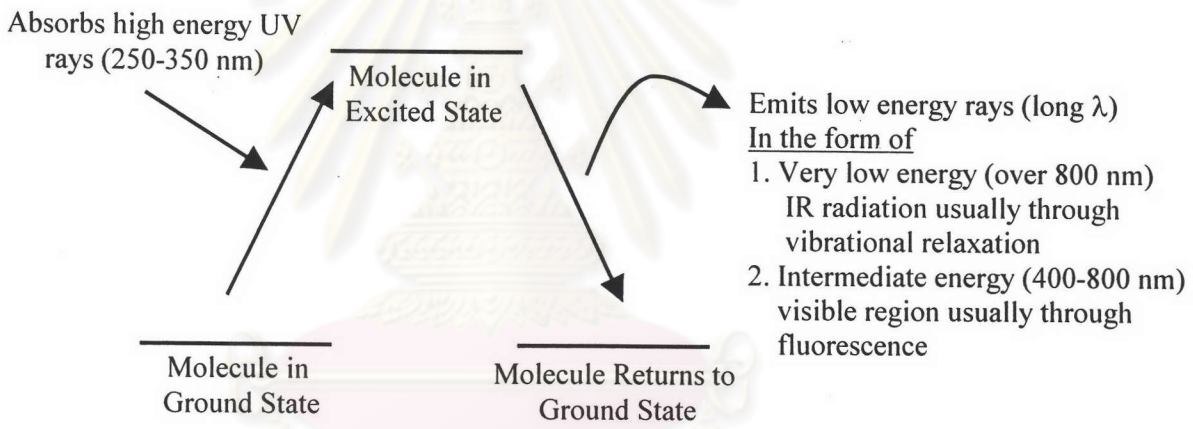


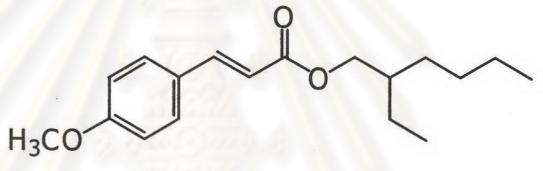
Figure 1.4 Schematic representation of the photophysical process of a sunscreen molecule.

1.3 Absorption of Sunscreens

The incidence of skin cancer in populations is similar to the overall incidence of all other cancers, and continues to increase. Although avoidance of long or intense sun exposure, shelter and protective clothing are the mainstay of skin-cancer prevention supplementary measures to lessen the harmful effects of sun exposure have also been sought. For many years the application of sunscreen to sun-exposed skin has been advocated as one such measure (12). Sun protecting substances are capable of protecting humans from harmful effects of solar radiation such as aging, sunburn (1),

UV-induced DNA damage (13,14) that causes the skin cancers. For example, in 2000 V. Bissonauth and coworkers (14) have shown that sunscreens can prevent simulated sunlight-induced epidermal disorganization. The frequencies of cyclobutane pyrimidine dimers, the photooxidative products, were significantly reduced by the sunscreen.

The ideal sunscreen should situate on skin (in epidermal layer) to help shielding the UV light, however, many reports have demonstrated transdermal absorption of organic UV filters including cinnamate derivatives. For instance, in 1995 U. H. Leweke and B. C. Lippold (15) detected the absorption of isoamyl-4-methoxycinnamate into the human skin. Similarly in 1997 C. G. J. Hayden and coworkers (16) reported that OMC was absorbed through the skin layers. In this study, OMC (**I**) could be recovered from milk of human volunteers.



(I)

F. Benech-Kieffer and coworkers (17) studied the percutaneous absorption of OMC sunscreens *in vitro*. OMC absorptions were detected in both pig and human. The correlation of the quantitative data between pig skin and human skin was very good. This research confirmed the OMC absorption through both pig's and human's skin layers.

Since sunscreen preparations are often applied on large skin area, therefore, low penetration rates can cause significant amount of chemical UV absorber to enter the body (18). Sun protecting preparations need to achieve a controlled release (19). For this purpose, liposomes, microsponges, microsphere, nanocapsules and inclusion complexes have been used (18-20).

1.4 Sunscreen Polymers

UV filters are also incorporated in sunscreens and into many everyday-use cosmetics such as moisturizers and lipsticks, in order to protect the skin from damage through UV radiation. Sunscreen preparations are usually applied superficially to

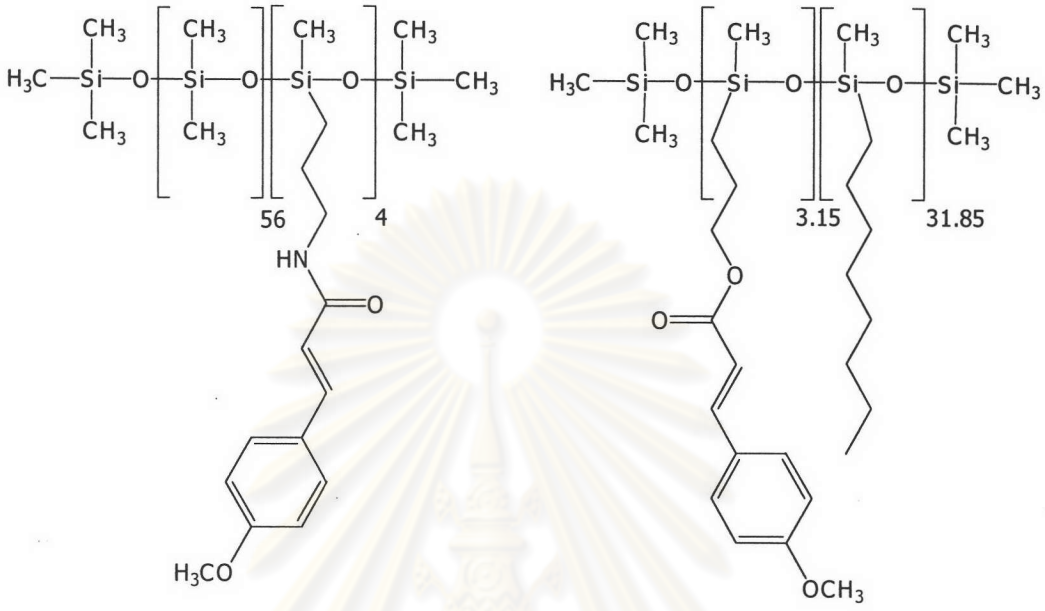
large skin areas. Therefore, effectiveness implies that sunscreen filters adhere to skin like a protective film. They should have a high affinity for the stratum corneum. The UV filters are designed to remain on the upper most layers of the skin; penetration through the skin should be low. For sunscreens to be effective, the UV absorbers must remain in the outermost regions of the skin. An ideal sunscreen product should exhibit high skin accumulation of UV absorbers with minimal permeation to the systemic circulation (21, 22).

At present, research as far as sunscreens are concerned moves towards the conception of new cosmetic formulas, which have a total innocuity, a small capacity to overcome the skin barrier, a good substantiality, and an important remanence.

Hence, sunscreen polymers are introduced as the new generation for cosmetics, especially for UV blockers for the use on human skin and/or hair. Various types of polymers have been tested because of their previously demonstrated safety with other applications. These large molecular weight compounds achieve almost no penetration beyond the stratum corneum, thereby limiting unfavourable side effects such as inflammation. Traditional polymeric enhancers have included benzalkonium chloride and hexadecylpyridinium bromide type polymers (PEG/PDMS) (23). Recently, the group of Nagase *et al.* has demonstrated the enhancing properties of polyethylene glycol or polydimethylsiloxane block copolymer with a cationic end-group (24). Furthermore, this polymer was shown to have enhancement activity for both hydrophilic and hydrophobic drugs. It was also demonstrated that the chain lengths of both the PEG and PDMS segments influenced the enhancing effects of the block copolymers.The authors suggested that the mechanism of action was limited to an increase in the partition coefficient at the skin surface rather than a change in the diffusion coefficient of the skin.

Although polymers described above do not absorb UV themselves, they help retain small UV filter molecules on the upper skin layers. Another approach is to make polymers with UV absorption property themselves. In 2004 S. Pattanaargson *et al.* (25) described the grafting of OMC absorption chromophore, 4-methoxy cinnamoyl moieties, onto silicone polymer to produce sunscreening polymer that can be effectively retained on skin surface. Both 3-(*p*-methoxycinnamido)propyl] (methyl) dimethylsiloxane copolymer, G-AS (**I**) and poly[(methyl)(octyl)(methyl) (propyl-4-methoxycinnamatesiloxane], G-MHS (**II**) (Figure1.5) exhibit UVB absorption profile similar to octyl methoxycinnamate (OMC). Photostability test revealed that G-AS and

(OMC). Photostability test revealed that G-AS and G-MHS were more photostable than free OMC. Moreover, skin absorption tests of both products suggested that skin permeation of the grafted chromophores were much lower than that of free OMC.

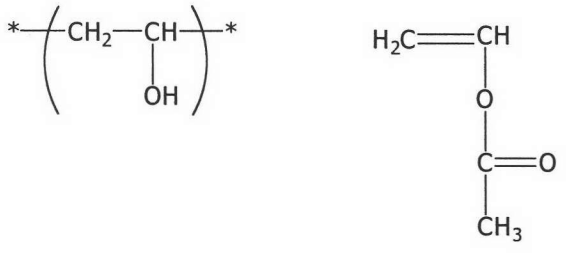


(I) **(II)**

Figure 1.5 Chemical structures of [3-(*p*-methoxycinnamido)propyl](methyl)-dimethylsiloxane copolymer, G-AS and poly[(methyl)(octyl)(methyl)(propyl-4-methoxycinnamatesiloxane], G-MHS respectively.

1.5 Poly(Vinyl Alcohol) (26)

Poly(vinyl alcohol), PVA (**I**) was commercialized over 50 years ago and has found extensive use in applications such as textiles, adhesives, and paper coatings. PVA is a synthetic, manmade polymer produced by the polymerization of vinyl acetate monomer, VAM (**II**).



(I) **(II)**

In general, the substantive properties of PVA relate to fundamental properties of their polymeric structures. The most important properties with regard to the production of all PVA manufactured worldwide are shown below.

PVA Properties: Effects of Hydrolysis—The application under consideration, PVA can be either eadily soluble or not soluble at all. The hydrolysis level of the PVA and various properties are shown in Figure 1.6

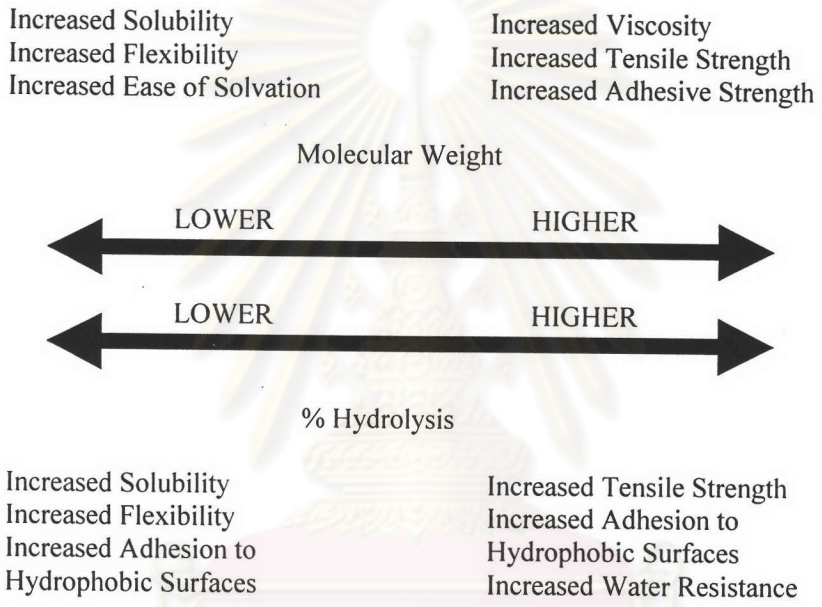


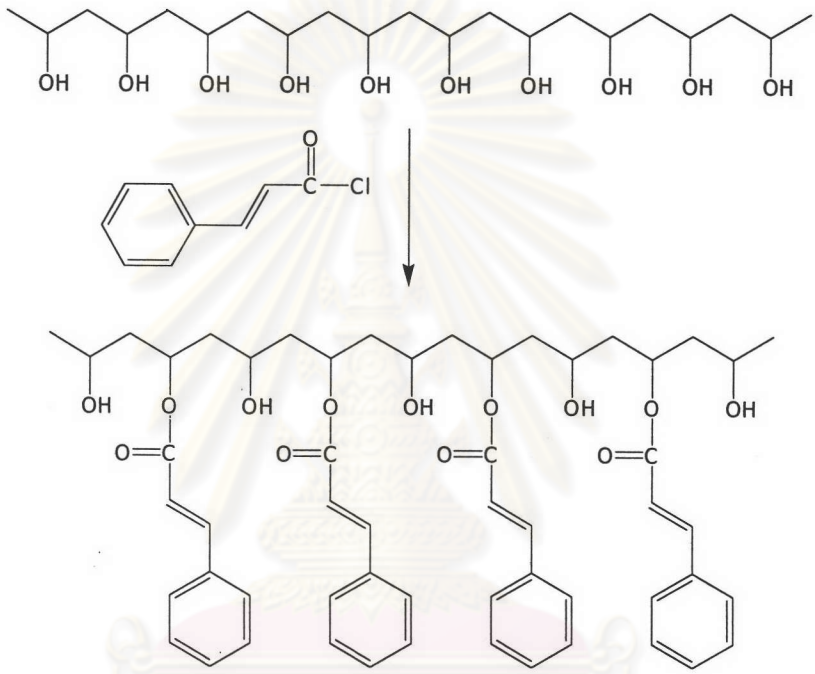
Figure 1.6 Describes the properties obtained by varying the hydrolysis and molecular weight of PVA.

Health Factor—PVA is an extremely safe chemical to both humans and the environment. For example, PVA is used in many food contact applications where it has been approved by the United States Food and Drug Administration (FDA), as well as other country's governmental bodies. It is also listed in the United States Pharmacopeia as a pharmaceutical aid. In fact, PVA is used as a controlled release mechanism on orally ingested pills. In addition, PVA is used as a component in: facial masks, hand cleaners, cold creams, cleansing creams and contact lens fluids. Moreover, extensive testing has indicated a very low order of toxicity when PVA was administered to laboratory animals.

The safety of PVA makes this polymer very population on various applications worldwide.

1.6 Poly(Vinyl Cinnamate) (27)

Poly(vinyl cinnamate), PVCN (**I**) is an interesting negative photoresist. This polymer is synthesized by the partial esterification of poly(vinyl alcohol), which itself is made by a polymer modification reaction (hydrolysis of poly(vinyl acetate)).



(I)

Figure 1.7 Synthesis of poly(vinyl cinnamate) by esterification of poly(vinyl alcohol).

The cinnamate groups undergo [2+2] cycloaddition when irradiated, leading to a crosslinked polymer suitable as a negative photoresist.

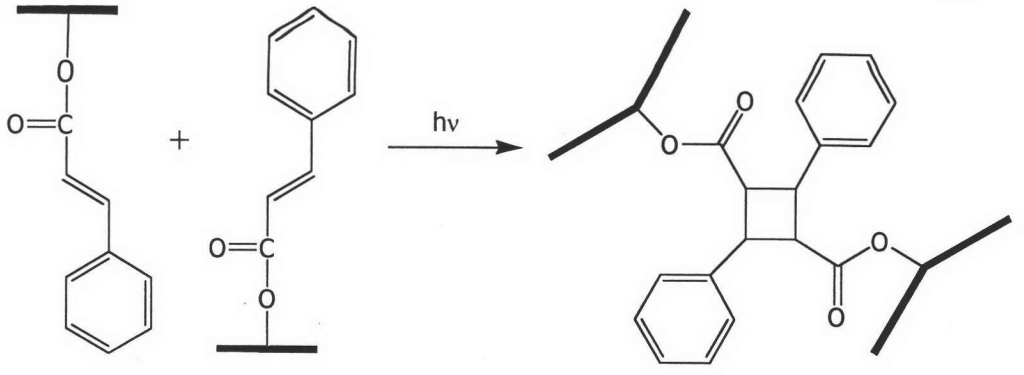
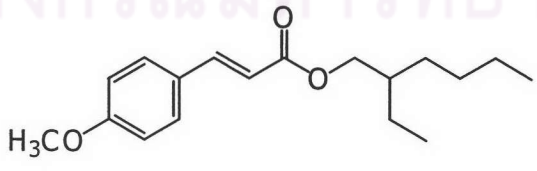


Figure 1.8 Photochemical reactions in PVCN [2+2] photocycloaddition.

1.7 Literature Reviews

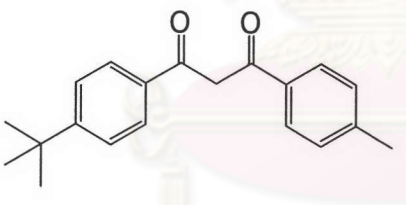
The rising level of awareness of the harmful effects of sunlight has fuelled a growth in the use of sunscreens. Sunscreen preparations contain organic chemicals which lessen the amount of UV light reaching human skin by absorbing the radiation. As mentioned earlier, the photoactivated sunscreen molecule disposes of the excitation energy in several ways: in the form of heat, by fluorescence, phosphorescence, interaction with neighbouring molecules or by undergoing photoinduced decompositions. The latter reactions not only decrease the sunscreen UV-protective capacity during usage but can also produce allergic or toxic degradation products. Therefore a high photostability is a prerequisite for the effectiveness of sunscreen products. 2-Ethylhexyl-*p*-methoxycinnamate (*trans*-OMC) represents the most widely used sunscreen compound. It is approved by the regulatory agencies of Europe (EEC Directive,1976), USA (US Food and Drug Administration,1999), Japan and Australia.



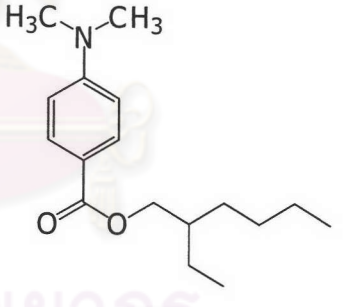
2-Ethylhexyl-*p*-methoxycinnamate (*trans*-OMC)

However, several studies have demonstrated that *trans*-OMC is unstable following irradiation both in solution and in emulsion formulations (28, 29).

For example, in 1995 J. Meijer and M. Loden (28) studied the stability of OMC in an ordinary sun lotion. Analysis of light exposed OMC at room temperature by reverse phase HPLC revealed a new peak with slightly lower retention time. This new peak was dramatically increased while the OMC peak was significantly decreased after more light exposure. The authors suggested a *cis-trans* isomerization of OMC based on the report of *cis* to *trans* photoisomerization of cinnamic acid. Similarly, in 1999 N. Tarras-Wahlberg and coworkers (29) reported that butylmethoxy dibenzoyl methane (**I**), octyl dimethyl PABA (**II**) and OMC were not stable against UV irradiation. Their UV absorbance decreased rapidly upon additional exposure to UV light. In 2001, S. Pattanaargson and P. Limpong (30) affirmed that a *trans* to *cis* configurational change of OMC does occur upon light exposure and its photoisomerized product, *cis*-OMC, was isolated (Figure 1.9) and its molar absorption coefficient (ε) was determinated. The ε value of *cis*-OMC is about only half of that of *trans*-OMC. This explains the decrease in absorption property of OMC upon UV exposure.



(I)



(II)

Additionally, kinetics study of *cis/trans* photoisomerization of OMC indicates that the photostationary equilibrium will shift to more *trans* configuration in more hydrophobic medium (31).

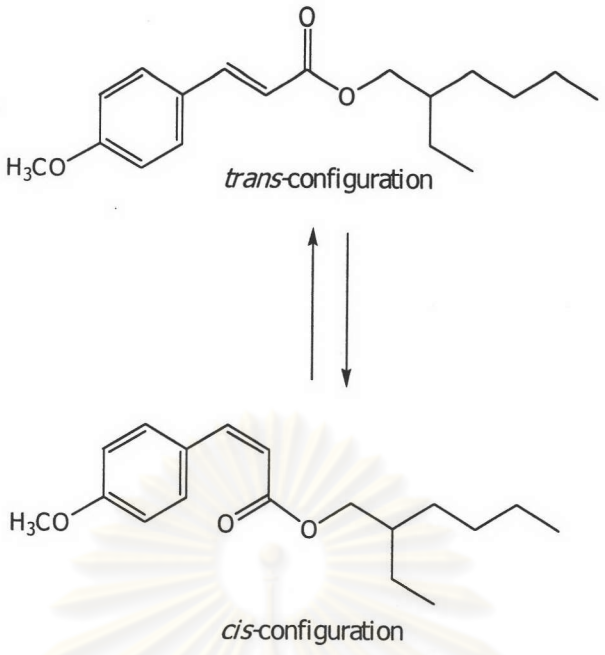
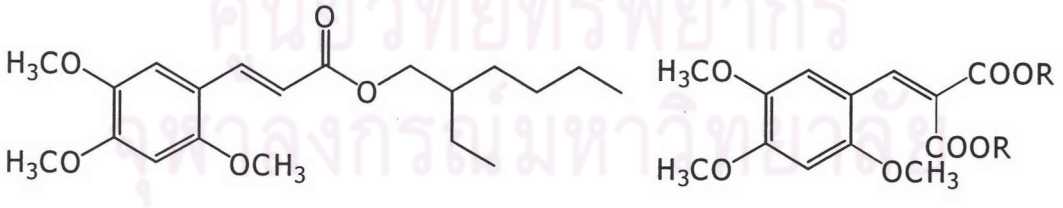


Figure. 1.9 Conversion of *trans*-OMC to *cis*-OMC after exposure to UV radiation.

In 2002 M. Thitinan synthesized various cinnamate derivatives and related compounds and studied their UV absorption properties. The 2-ethylhexyl-2,4,5-trimethoxycinnamate (**III**) and all dialkyl-2,4,5-trimethoxy benzalmalonates (**IV**) (Figure 1.10) showed UVA and UVB screening properties, irritation test of the compounds on volunteers were performed. Results showed promising prospect of this newly developed UV filter (32).



(III) **(IV)**

Figure 1.10 Chemical structures of 2-ehylhexyl-2,4,5-trimethoxycinnamate and all dialkyl-2,4,5-trimethoxy benzalmalonates respectively.

1.8 Research goal

Although OMC is the most popular sunscreen in cosmetic industry nowadays, as mentional earlier, it still possesses few problems including absorption through human skin and the photounstability. Few methods have been proposed to reduce skin penetration of sunscreen (17-20). However, transdermal permeation of the sunscreens cannot be totally blocked. We propose here, the preparation of A) sunscreen polymer that is a grafted product of UV absorbing chromophore onto poly(vinyl alcohol) and B). With higher molecular weight of the resulted UV absorbing polymer comparing to the conventional small UV filtering molecule, transdermal absorption should be considerably decreased.

The objectives of this research can be summarized as follows:

1.8.1 To synthesize diethylbenzalmalonate vinyl ether monomer and to prepare poly(diethylbenzalmalonate vinyl ether) from such monomer.

1.8.2 To graft the UV filter chromophore; 2,4,5-trimethoxycinnamic acid onto poly(vinyl alcohol).

1.8.3 To determine absorption wavelength, molar absorptivity and photostability of the synthesized materials.