

CHAPTER I

INTRODUCTION

Ultraviolet radiation (UVR) includes the region of the electromagnetic spectrum between visible and x-rays. UV radiation is subdivided into the UVA (400 to 320 nm), UVB (320 to 290 nm) and UVC (290 to 200 nm).

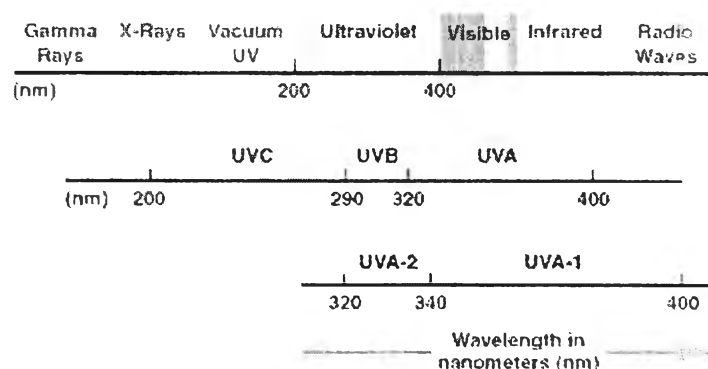


Figure 1.1 The total spectrum of radiant energy¹

UVR at the earth's surface comprises approximate 95% UVA and 5% UVB. Intensity of surface UVR depends on factors such as solarisation angle, time, season, latitude and others. UVC radiation does not reach the surface of the earth because it is absorbed by the earth's ozone layer. This is a very important fact because UVC is highly damaging to living cells.

UV Radiation plays a major role in the pathogenesis of a sunburn reaction, skin cancer and photoaging of human skin. People who live in areas of greater UVR exposure (semitropical and tropical areas) have a much greater risk of developing non-melanoma skin cancer than those living further from the equator.²

1.1 Effect of ultraviolet radiation on the skin³

Skin, the largest organ in the body, has several functions such as regulation of body temperature, protection the body from the environment, partial regulation of water loss and other biochemical properties.

Skin can be subdivided into 3 layers, the stratum corneum, epidermis and dermis. The dermis contains melanocytes, special cells those produce melanin through UVA stimulation. Melanin then, acts as a protective layer scattering away harmful radiation from the skin. Figure 1.2 shows the amount of UV radiation that penetrates each skin layer. UV Radiation near 300 nm (UVB) penetrates both the stratum corneum and the epidermis and is energetic enough to cause severe burning (erythema) of the skin, especially in fair-skinned individuals. Radiation higher than 300 nm starts penetrating the third layer, the dermis, thereby stimulating the formation of melanin, producing a tan that protects the skin from an immediate sunburn. Unfortunately, besides stimulating the formation of melanin, UVA can cause other harms such as elastosis and formation of singlet oxygen species.³

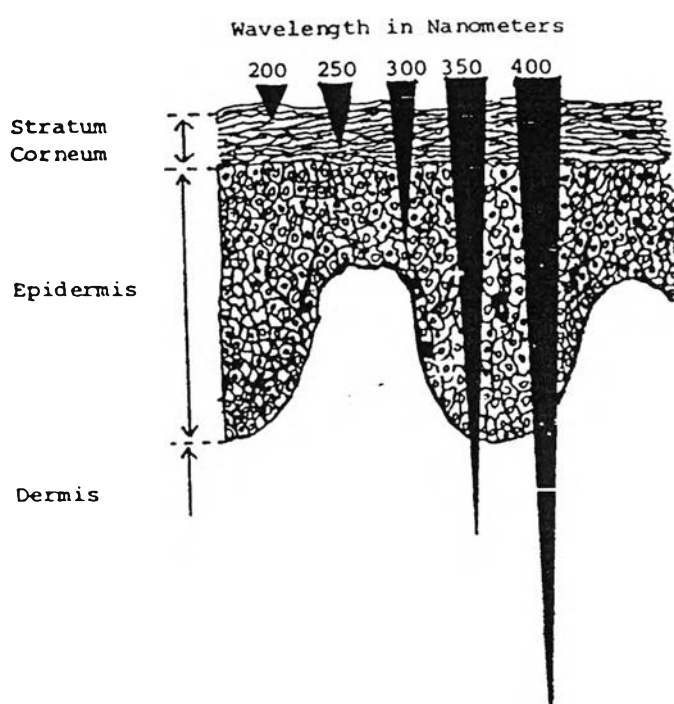


Figure 1.2 Schematic representation of light penetration into the skin³

1.2 Classification of UV filters

UV Filters (or sunscreen agent) not only can alleviate the carcinogenic potential of solar radiation but also can minimize other damaging effects of UV exposure. As a result there is a widely use of such agent to protect human skin from various harmful effects of ultraviolet radiation.

UV Filters can be classified into two main categories: physical blockers (inorganic or mineral filters) and chemical blockers (organic or chemical filters).

A. Physical blockers

The physical blockers are chemicals that reflect or scatter the ultraviolet radiation. Examples of physical blockers include zinc oxide, titanium dioxide and red petrolatum. Physical blockers, if present in sufficient quantities, will reflect all the ultraviolet, visible and infrared rays. They are used in conjunction with chemical absorbers to achieve high sun protection factor (SPF).

B. Chemical absorbers

The chemical absorbers absorb the harmful ultraviolet radiation. They are classified into either UVA or UVB blockers, depending upon the type of radiation they can absorb. Sunscreen chemicals are generally aromatic compounds conjugated with carbonyl groups in their structures.

Table 1.1 UV Filters currently used in the sun care industry⁵

| Medicinal Ingredient | Synonyms | Maximum Concentration (%) |
|---|---|---------------------------|
| Ethyl dihydroxypropyl PABA | 4-Ethyl-[bis(2-hydroxypropyl)amino] benzoic acid | 5 |
| Octyl methoxycinnamate | 2-Ethylhexyl methoxycinnamate | 8.5 |
| Homosalate | Homomenthyl salicylate | 15 |
| Padimate-O | Octyl dimethyl PABA | 8 |
| 2-Phenylbenzimidazole-5-sulfonic acid | - | 8 |
| Oxybenzone | Benzophenone-3 | 6 |
| Sulisobenzene | Benzophenone-4 | 10 |
| Dioxybenzone | Benzophenone-8 | 3 |
| 2-Ethylhexyl salicylate | Octyl salicylate | 6 |
| Triethanolamine salicylate | Trolamine salicylate | 12 |
| Titanium dioxide* | Titanium oxide | 25 |
| Menthyl anthranilate | Menthyl 2-aminobenzoate | 5 |
| Octocrylene | 2-Ethylhexyl-2-cyano-3,3-diphenylacrylate | 12 |
| Terephthalylidene dicamphor sulfonic acid | 3,3'-(1,4 phenylenedimethylidene)bis [7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptylmethanesulfonic acid | 10 |
| Cinoxate | 2-Ethoxyethyl <i>p</i> -methoxycinnamate | 3 |
| Butyl methoxy dibenzoylmethane | Avobenzene | 5 |
| Glyceryl PABA | Glyceryl <i>p</i> -aminobenzoate | 3 |
| PABA | <i>p</i> -Aminobenzoic acid | 15 |
| Diethanolamine methoxycinnamate | - | 10 |
| 4-Methylbenzylidene camphor | - | 6 |
| Zinc oxide* | - | 20 |

*Physical sunscreen. acceptable UVA/UVB block

1.3 Mechanism of chemical absorber

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 other words, these molecules contain conjugated systems those allow electron delocalization upon absorption of photons. They absorb the harmful (high-energy) UV rays (250-400 nm) and convert the absorbed energy into innocuous longer wave (lower-energy) radiation (usually above 400 nm). Figure 1.3 shows the mechanism of UV-absorbers.

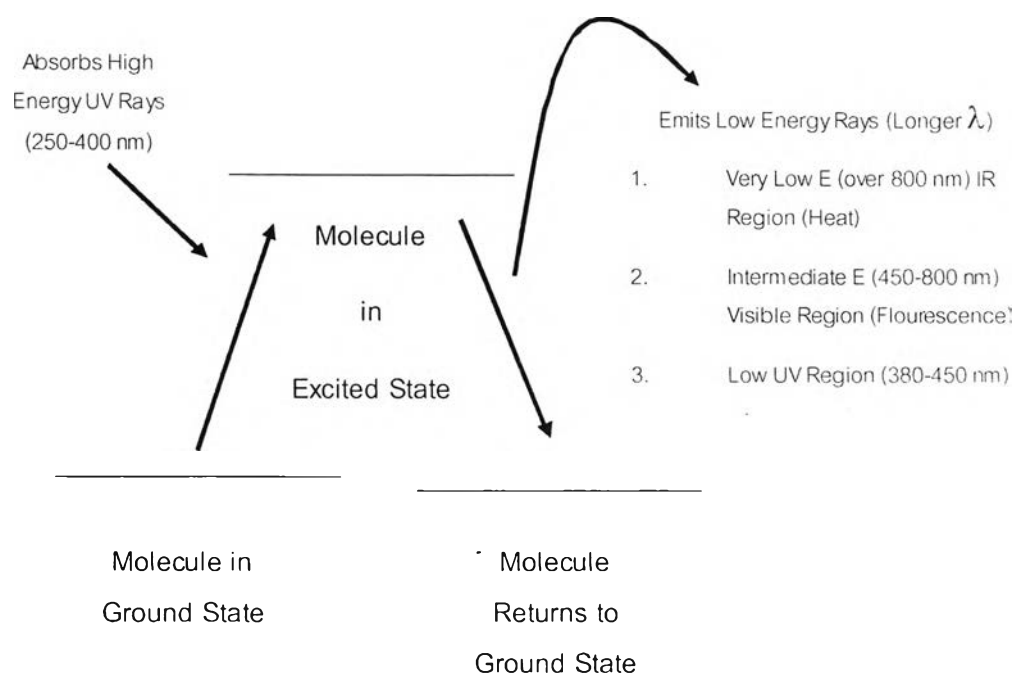


Figure 1.3 Schematic representation of process in which a sunscreen chemical absorbs the harmful high-energy rays and renders them relatively harmless low energy rays³

1.4 Effect of vehicle on the ultraviolet absorption of UV filters

1.4.1. Effect of pH

The UV absorption spectra of acidic and basic compounds may be affected by pH. For acidic compound, such as phenol, the use of alkaline conditions (pH over 9) will assist the formation of anions that tend to increase delocalization of electron. This electron delocalization would decrease the energy required for the electronic

transition in the UV spectrum; hence, a bathochromic shift is observed (longer wavelength or λ_{\max}). In the opposite manner, acidic conditions (pH below 4) will assist the formation of cations for aromatic amines. A hypsochromic shift towards lower wavelength occurs because the protonation of the unbounded lone pair of electrons will prevent any resonance delocalization of the electrons.

1.4.2 Effect of solvent

The use of different solvents in cosmetic formulations may profoundly influence the effectiveness of a sunscreen chemical. The shifts in the ultraviolet spectrum are due to the relative degrees of solvation of the ground state and the excited state. The solvation of polar sunscreen (e.g., PABA, benzophenones) with polar solvents, such as water and ethanol, will be quite extensive. When this solvent stabilization is more pronounced for the ground state than for the excited state, a hypochromic shift to the shorter wavelength will be observed. This is often the case for polar sunscreen in polar solvents. On the contrary, for less polar sunscreen compounds (e.g., octyldimethyl PABA, cinnamate) the solvent-solute interaction (hydrogen bond) is often different because the excited state is more polar than the ground state. The net result is, therefore, a stabilization of the excited state by polar solvents. This lowers the energy gap of the electronic transition between the ground state and the excited state, hence, a higher λ_{\max} or a bathochromic shift would be expected.

1.4.3 Effects on the extinction coefficient

A value of the extinction coefficient (ϵ) is the basis on which the effectiveness of a sunscreen chemical is assessed. Therefore, chemicals with a high extinction coefficient are more efficient in absorbing the harmful UV radiation than chemicals with a lower extinction coefficient.

All electronic transitions for any compounds can be characterized as symmetry allowed or symmetry forbidden. Symmetry-allowed transitions generally have high extinction coefficients, and symmetry-forbidden transitions have lower extinction coefficients. The extinction coefficients for sunscreen chemicals can be arrived qualitatively by studying both the spatial requirements and the electronic transition responsible for the observed UV spectrum. The degree of resonance delocalization in

a molecule can be used to predict the relative λ_{\max} . It is also possible to qualitatively predict an extinction coefficient value from the degree of resonance delocalization in a molecule.

1.5 Absorption of sunscreen

Safety of sunscreens has remained a major topic of discussion, so several reports have appeared in the literature regarding allergy and photoallergy to sunscreens. Only few photoallergic reactions induced by 2-ethylhexyl-*p*-methoxycinnamate (OMC)⁶⁻⁷, the most widely used sunscreen agent have been reported. This compound, although, has large molar absorptivity (ϵ), transdermal absorption of OMC was detected. There are many reports on the absorption and distribution of OMC. In 1995, J.Hanny and R.Nagel⁸ reported the detection of sunscreen agents in human breast milk. This report is consistent with the study in 1995 by U.H.Leweke and B.C.Lipold⁹ in which transdermal penetration through human skin layer of various sunscreens were evaluated. In 1997 C.G. Hayden and coworkers¹⁰ could not detect OMC in urine of volunteers after applied a commercially SPF15+ sunscreen product to surface of their forearms. This study indicated the hydrophobic nature of OMC and agreed with the facts that OMC was found in breast milk.

In 1999, V.K.Gupta and coworkers¹¹ studied absorption of sunscreen through Micro-Yucatan Pig skin *in vitro* and evaluate the influence of different formulation by diffusion cell technique. They observed that OMC reached the stratum corneum layer (SC) within an hour and the amounts penetrated into viable skin and receptor fluid increased slowly over time. Hydro-alcoholic and oil base, diisopropyl adipate, vehicle formulation showed different penetration rates. OMC Transdermal penetration through human skin was also demonstrated in other studies including work done by G.Potard group¹²⁻¹³ and V.Savveiga group¹⁴.

1.6 The development of ultraviolet absorbers

Skin cancer is the most common type of cancer in the world today, so the use of topical sunscreen is recommended as a mean of protecting the skin against ultraviolet radiation and protecting skin cancer. In addition to the UV filtering efficiency of a UV filter itself, controlling of the concentration and distribution of

those UV filters in the corneum layer is also a key to optimize its benefit.¹⁵ The sunscreen substances show a loss of their specific function when penetrating the skin surface and thus the penetration of these ingredients must be avoided. Several attempts have been made to quantify the amount of UV-absorbing chemicals which enter the body via skin. The developments of new ingredients and new delivery systems have been developed to increase the skin accumulation of UV filtering agents. For this purpose, D. Fairhurst and M. Mitchnick¹⁶ encapsulated the organic sunscreen into a polymeric matrix. In 2002, D.A.Godwin et al.¹⁷ determined the influence of Transcutol[®]CG (diethylene glycol monoethyl ether) which was added in sunscreen formulation on the transdermal permeation and skin accumulation of sunscreen octyl methoxycinnamate (OMC).

Solid lipid microspheres (SLM) which is another controlled release system was applied to OMC by G.Yener and coworkers¹⁸. In this work, they prepared solid lipid microspheres of octyl methoxycinnamate (OMC) and studied the release, penetration, and photostability of OMC in SLM .

The vehicle's nature usually can influence the penetration profile of active ingredients. The nanocapsule (NC) has been a very attractive cosmetic active vehicle. In 2004 group of M.M. Jimenez¹⁹ investigated the influence of the carrier NC on *the vitro* absorption of OMC by comparing between oil-in-water and water-in-oil emulsion of free-OMC and OMC entrapped in NC (OMC-NC). Among these, OMC-NC showed the least penetration.

An alternative strategy to reduce the penetration of UV absorber is to increase the size of sunscreen molecule. In 2004, S. Patanaargson et al.²⁰ described the grafting of OMC absorption chromophore, 4-methoxycinnamate moieties, onto silicone polymer to produce sunscreensing polymer. The study of photostability test revealed that the grafted polymers were more photostable than free OMC and skin permeation of such polymer was much lower than free OMC.

Another methodology in reducing sunscreen transdermal absorption is to use less UV filter in the formulation. This can be done by using SPF enhancer. SPF Enhancer can increase the skin's protection ability with less amount of UV absorber used. This method was demonstrated by P. Hossel et al.²¹ in which the N-vinylimidazole polymer was prepared and used as SPF enhancer in the formulation.

1.7 Condensation polymerization²²

One classification divides polymers into condensation and addition polymers, and the other divides them into step and chain polymers. The condensation-addition classification is primarily applicable to the composition or structure of polymers. The step-chain classification is based on the mechanism of the polymerization reactions.

Condensation polymers were polymers that formed from polyfunctional monomers by the various condensation reaction of organic chemistry with the elimination of some small molecule such as water.

All step polymerizations fall into two groups depending on the type of monomer(s) employed. The first involves two different bifunctional and/or polyfunctional monomers in which each monomer possesses only one type of functional group. (A bifunctional monomer is a monomer containing two functional groups per molecule. A polyfunctional monomer is one with three or more functional groups per molecule.) The second involves a single monomer containing both type of functional groups.

Step polymerizations proceed by the stepwise reaction between the functional groups of reactants as in reactions. The size of the polymer molecules increases at a relatively slow rate in such polymerizations. One proceeds slowly from monomer to dimer, trimer, tetramer, pentamer, and so on until eventually large polymer molecules containing large numbers of monomer units have been formed. Any two molecular species can react with each other throughout the course of the polymerization. The situation is quite different in chain polymerizations where full-sized polymer molecules are produced almost immediately after the start of the reaction (Fig. 1.4).

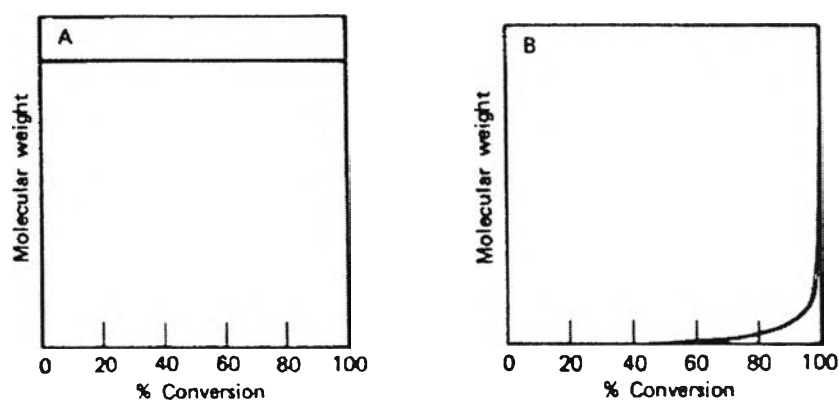


Figure 1.4 Variation of molecular weight with conversion. A, chain polymerization; B, step polymerization²²

1.7.1 Polyester

Common polymers are synthesized by step polymerization. Usually common methods used in synthesizing simple esters are used to make polyesters. These include direct esterification, transesterification and the reaction of alcohols with acyl chloride or anhydrous.

Simple esterification is a well-known acid-catalyzed reaction and polyesterification follows the same course. The reaction involves protonation of the carboxylic acid.

The cationic-exchange resin-catalysed esterification is another acceptable method of making an ester. In 2002, G.D. Yadav and M. Ranuman²³ studied the catalytic activity of cation-exchange resin as the catalyst in esterification. The order of activity was found to be as follows: Amberlyst-36>Bayer K2241>Amberlyst-15>Dowex 50Wx8>Indion-130>Deloxane ASP>Filtrol-24>K-10 Montmorillonite.

Lipases have been used as biocatalysts for intra-esterification²⁴, interesterification²⁵ and lactonization²⁶. In 2003, S. Haam and coworkers²⁷ studied enzymatic esterification of β -methylglucoside with acrylic/methacrylic acid in organic solvents. In 1997, group of A. J. Russell²⁸ investigated solvent-less copolymerization of divinyl adipate and 1,4-butanediol using Novozyme-435 (*Candida antartica* Lipase B on Lewatit) as a catalyst. The obtained polyester showed M_w of 23,200 g/mol. R.A. Gross and coworkers²⁹ studied bulk condensation polymerization of adipic acid and octanediol, catalyzed by *Candida antartica* Lipase B (CALB). In 2005³⁰ they prepared one-pot enzymatic syntheses of both linear and hyperbranched copolymer containing glycerol.

In 2000, Z. Mouloungui and C. Lacaze-Dufaure³¹ studied the reaction between oleic acid and 2-ethylhexanol. They found that a reaction containing 1% para-toluene sulfonic acid (*p*-TSA) in xylene could be complete in 50 minutes at 140°C while 93% of ester could be reached after 10 minutes in alcoholic medium containing 1% *p*-TSA. Without added catalyst, the reaction was completed in 280 minutes at 170°C in the alcoholic medium. Several examples of polyesterification have been reported using *p*-toluene sulfonic acid as an acid catalyst.³²⁻³³

In 2005, A. Takasu, A. Takemoto and T. Hirabayashi³⁴ studied a direct dehydration polycondensation of dicarboxylic acids and diols in water by surfactant-combined catalysts. *p*-dodecylbenzenesulfonic acid (DBSA) and a subsequent chain

extension in the emulsion, scandium Tris(dodesyl sulfate). This procedure did not require a removal of water, because the esterification was established at the interface of the emulsion in water. The polyester ($M_w=10.1\times 10^3$) could be prepared from esterification between 1,9-nonanediol and dodecanedioic acid (the molar ratio of dicarboxylic acid to diol = 1:1) using 16wt% DBSA.

1.7.2 Polymer with cinnamate

The polymers with cinnamate groups have attained much attention because of they have a reactive photosensitive function to apply in emerging fields such as liquid crystalline display, microelectronics, photocurable coating, etc. The former is a photopolymer containing the cinnamate pendant group.

In 1994, F.Scigalski and coworkers³⁵ have studied a class of light sensitive polymers. They attached *o*-, *m*- and *p*-hydroxycinnamate group on to poly(styrene-*co*-2-bromoethyl methacrylate) and chloromethylated polystyrene as pendant groups. The photochemical properties of these polymers were then studied. Polymer containing cinnamate moiety are usually found used as photo-mark and negative resist.³⁶

Cinnamate group is well-known for the dimerization reaction by ultraviolet irradiation and their anisotropic dimerization are used for aligning liquid crystals. The flexibility of polymer might also be related to the photo-dimer orientation and liquid crystals (LCs) alignment. In 2004, S. Sung and coworkers³⁷ prepared two polymer with cinnamate pendant group with different chain flexibility and investigated the effect of chain flexibility of polymers. Poly(3-ethylene-*alter*-1-vinyl cinnamate), PEVCi, have larger spacing between cinnamate moiety than poly(vinyl cinnamate), PVCi, two cinnamate polymers show different behavior of thermal reaction of cinnamate moiety. PVCi shows no change of FT-IR peaks after heating. Whereas, PEVCi shows the same change of FT-IR spectra with the case of UV irradiated PEVCi. The changes of carbonyl band from conjugated position ensure the dimerization reaction of both cinnamate polymers.

1.8 Research goal

Although *p*-methoxycinnamate is the widely used organic UV filter, there is no application of polymer containing such group as polymeric UV filter. In this work, however, oligomers containing *p*-alkoxycinnamate as repeating units were prepared.

Studies of photodimerization, UV-absorption, photostability and solubility were conducted.

The aim of the work was to prepare oligomeric material with UV-absorption property. Our attention was not only paid to the UV filtering property, transdermal absorption and photostability of the synthesized oligomers but also other physico-chemical properties of the materials including melting point and solubility were clearly monitored. This is because these later properties are equally important for the application of the materials to any cosmetic formulation.